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ON THE LENGTHENING AND SHORTENING REACTIONS AND THEIR OCCURRENCE IN MAN.

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MUSCLES with intact innervation have the capacity to bear:—

I. Different weights at the same length.

II. The same weight at different lengths.

These two functions can be achieved voluntarily but also reflexly, the first being brought about by the stretch reflex, the second by the lengthening and shortening reactions.

It has been demonstrated by Sherrington and Liddell that by a passive stretch sensory end-organs in the muscle are stimulated, with the result that these end-organs respond by producing impulses which excite a reflex contraction of the stretched muscle, so that its tension increases ("stretch reflex or myotatic reflex"). In order to bear the weight by which the muscle is stretched, the tension of the muscle must become equal to the weight. If the tension does not increase by the stretch reflex till it is equal, then the weight will drop, and the muscle will be still more lengthened, with the result that the stretch reflex comes again into play, so that still more muscle-fibres (more motor units) are reflexly thrown into contraction, and the tension increases once more. It may be that in this way it is brought about that a muscle can bear a heavier load without being passively much lengthened.

However, it has been observed by Sherrington and Liddell that in the decerebrate cat a stretch of less than 1 mm. of the m. quadriceps may give a contraction developing more than 2 kg. tension; that is to say a tension equal to the average weight of the cat, whereas a stretch of 7 mm. may produce 4 kg. tension! In order to produce a passive stretch of less than 1 mm., it is, however, not necessary to load the quadriceps with a weight of more than 2 kg., but this will already be achieved by a much smaller

weight. It is obvious therefore that a passive stretch by a definite load may give reflexly an increase of the tension which exceeds the weight of the load. As soon as the tension has become greater than the weight of the load, the latter will be raised, and if thereby the tension does not diminish, this will progress till the contracting fibres are maximally shortened. This, however, has never been observed. It seems therefore that the tension, produced by the stretch reflex, decreases when the muscle-fibres are shortened by the reflex contraction.[1] If by this decrease the tension has become less than the weight of the load, then the latter drops, so that the muscle is stretched again and the stretch reflex comes once more into play, with the result that the downward movement of the load is checked. It is presumably in this way, that is to say by the combination of the stretch reflex and its inhibition or disappearance during the reflex shortening of the muscle, that a regulation is reached which ensures that the loaded muscle is passively not much lengthened, nor reflexly much shortened, in other words, a regulation which brings about that a muscle can bear a heavier load by retaining almost its original length.

The Shortening Reaction.

In 1909 Sherrington published the following observation: "Subsequent to spinal transection, either thoracic or cervical, and after the period of spinal shock has passed, there are obtainable from the extensor muscle of the dog's knee some reactions, unmentioned in the literature, which appear significant for reflex co-ordination. Of these reactions one can be elicited and observed as follows: The animal is held supported under the shoulders with the hind-feet hanging free. Suppose the right limb to be examined: the observer lifts the knee of that pendent limb by simply supporting it from beneath under the tibial component of the joint. In this way the knee is raised with the knee-joint itself extended, but with the hip flexed. It is then found that the extensor muscle of the knee exhibits a considerable tonic contraction; if the supporting hand be shifted

[1] It may be supposed that this decrease of the tension is brought about because the sensory end-organs, providing the impulses of the stretch reflex, are thrown out of action by the shortening of the muscle fibres. Matthews was able to isolate a single muscle spindle in the small muscles of the toe of a frog and found, when the muscle was placed under slight stretch, that the spindle discharged continuously. When, however, the muscle itself was caused to contract, the responses of the muscle spindle *immediately ceased*. Other observations have led to the view that by the shortening of contracting muscle fibres other sensory end-organs are stimulated which respond by producing inhibitory impulses eliciting a central inhibition of the stretch reflex.

upward so as to no longer support the tibial part of the joint, the knee still remains extended, its extended posture being maintained by the tonic contraction of the extensor muscle. This much is obvious to inspection, but can be appreciated better if the observer attempt to forcibly flex the knee. The extensor muscle then opposes the forced flexion, and a considerable resistance to the flexion is experienced. This reaction may be termed, for brevity, the "shortening reaction."

The shortening reaction is frequently accompanied by a crossed reaction at the opposite knee. At this opposite knee the tonus of the extensor is relaxed and the knee undergoes flexion. The latency of this crossed effect is relatively long.

But this crossed flexion of knee is not a regular accompaniment of the shortening reaction; sometimes no crossed reflex accompanies it, and sometimes, according to Sherrington, it is accompanied by a crossed extension instead of crossed flexion.

The shortening reaction is also obtainable in the decerebrate animal. Starting with the hind-limb in the posture of extension, due to the decerebrate rigidity, the knee is to be first forcibly flexed. If from the flexed posture it is moved back to an extended posture, the knee is found on its release to remain extended; it remains extended not quite to the full to which the manipulator moved it, but yet extended far more than it had been in the flexed posture it was moved from. There is, however, a difference between the shortening reaction as observable in the decerebrate and in the spinal animal respectively. In the latter it is less easy to grade the extent of the reaction. For instance, although it is easy to change the posture of the knee from one of tonic flexion to one of extension, it cannot so easily in spinal animals be made to retain intermediate postures.

In the decerebrate animal the shortening reaction of the extensor of the knee still occurs when in the hind-limb all other muscles are thrown out of action by detachment from their insertions or by severance of their nerves, so that the vastocrureus muscle, with its nerve-branch, remains the sole nerve-muscle component intact in the whole limb. The shortening reaction is obtainable from the animal either supine or on its side, and the animal being supine the reaction is still brought about when a weak spring is attached to the leg below the knee in such a way that the spring is stretched by the passive extension of the knee.

If the ends of the vastocrureus are approximated by the passive extension of the knee then, according to Sherrington, the muscle is slackened, but only momentarily, for it quickly adjusts its length and "stays put," so holding the limb at the angle imposed. Sherrington has put forward

the view that the approximation of the end-points of the knee-extensor produces a reflex-contraction of this muscle and that "the bringing nearer together its insertion and origin appears to induce in the muscle a heightened tonus,"[1] by which the passively given posture is retained.

Fulton, however, has suggested that it is the passive stretch of the muscle, produced by the drop of the released limb, which excites the tension, by which the new posture is maintained. According to this view the shortening reaction is brought about by the stretch reflex. It has been observed by Samojloff and Kisseleff that in the decerebrate cat the action currents of the quadriceps decrease or disappear altogether, when the end-points of the muscle are passively approximated. In other experiments these authors have stretched the quadriceps first to a certain length x, and then to a greater length y, after which the stretch was lessened till the length x was reached again. It was thereby observed that the stretch to the length x entailed an increase of the action currents, which was followed by a further increase on stretching to the length y. On lessening the stretch a sharp decline of the action currents occurred, with the result that on reaching the length x again the action currents were much smaller than after the previous stretch to this length. This observation shows that in a passively lengthened muscle the strength of the action currents are at a definite length of the muscle much smaller if this length is reached by a stretch followed by a passive shortening than when the same length is reached by a simple stretch only. From these results the authors were led to the conclusion that the passive approximation of the end-points of the knee-extensor elicits a reflex-inhibition, by which the stretch reflex, and also the tension of the muscle due to the decerebrate rigidity, is inhibited.

Samojloff and Kisseleff agree with Fulton that the shortening reaction is excited by the passive lengthening of the muscle produced by the drop

[1] This is in agreement with the generally accepted view that a shortened muscle has a heightened tonus. If, for instance, after the removal of the right cerebral hemisphere and the animal being supine the left limbs are more extended than the right ones, it is generally accepted that the tonus of the extensors of the left limbs is heightened, that the extirpation has produced a left-sided hypertonia. In every posture, however, the tension of a muscle is equal to its load. As well in the extended as in the semiflexed posture of the hind-limb the load of the knee-extensors is the weight of the leg below the knee. In the extended limb this load is acting by a smaller level. Therefore, in the extended limb the tension of the knee-extensors is not greater, but even smaller than in the semiflexed one! In every posture the tension is only heightened when the load is heavier, for instance by a contraction with increased tension of the antagonists.

of the released limb, but, according to their view, this occurs after a previous reflex-inhibition elicited by the passive shortening of the muscle; in other words they suggest that the shortening reaction is due to a stretch reflex succeeding a previous inhibition. If the tension of a muscle is greater than the weight of its load the latter is raised, when the tension is less than the weight of the load the latter drops. It is therefore certain that in the new posture produced and maintained by the shortening reaction the tension is equal to the load. As has been mentioned above, it was observed by Sherrington that the shortening reaction still occurs when a spring is attached to the limb below the knee. The animal being supine and the spring not being attached the weight of the load, and therefore also the tension of the knee-extensor in the new posture, is equal to the weight of the limb below the knee, whereas the spring being attached the tension of the knee-extensor is equal to the weight of the limb below the knee + the tension of the spring.

The muscle does not "know" the load which it has to bear after the release of the limb, and still after this release its tension is equal to the load. This proves that it is the load itself which determines the tension of the muscle. It is apparent therefore that the shortening reaction, that is to say the retaining of the new passively induced length, is due to the stretch by the load, thus, in other words, by the stretch reflex, whereas it seems that the passive shortening previous to the release of the limb entails a decrease of the previous existing tension. The occurrence of the shortening reaction indicates that the sensory end-organs, which are stimulated by a passive stretch of the muscle, are able to respond *by any length* of the muscle.

The shortening reaction can also be obtained in man, and it can best be observed and analysed in children with marked idiocy accompanied by slight or moderate rigidity of the legs. In these cases it is certain that the reaction is reflexly, and not voluntarily, brought about.

The shortening reaction is obtainable if the child is held in the air supported under the shoulders (fig. 1), and also when it is supine (fig. 2) or lying ventrally. In these children the shortening reaction, or the passive extension, of one of the legs is sometimes accompanied by an extension of the crossed leg. With the child lying ventrally it can often be observed that the shortening reaction of the legs is also accompanied by a raising of the head. It was observed by Sherrington that in the decerebrate cat the shortening reaction is sometimes accompanied by a crossed extension, but more frequently by a crossed flexion. The latter reaction was never noted in the idiot children.

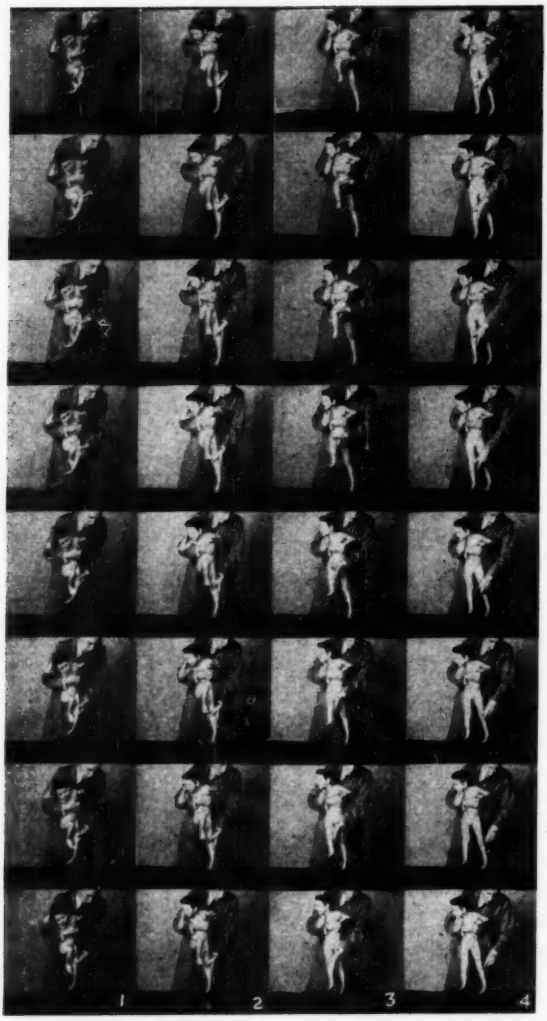

FIG. 1.—(1) Idiot child, held in the air supported under his shoulders. Both legs are kept in flexed posture. (2) First the left and then also the right leg (3) is passively extended. (4) Both legs retain the posture of extension.

FIG. 2.—(1) The child, being supine, keeps his legs also in the posture of flexion. (2-3) After passive extension the legs remain in the extended posture. (4) This posture is still retained, when the legs are lifted by a hand under the knees.

THE LENGTHENING REACTION.

Sherrington has noted in the chronic spinal animal another reaction, in several respects the converse of the above shortening reaction, which he described as follows: "Suppose the shortening reaction to have been evoked and the extended posture of the knee due to the tonic contraction of the extensor to be going on. If the observer, then, with one hand still supporting the lower end of the thigh, take with his other the leg

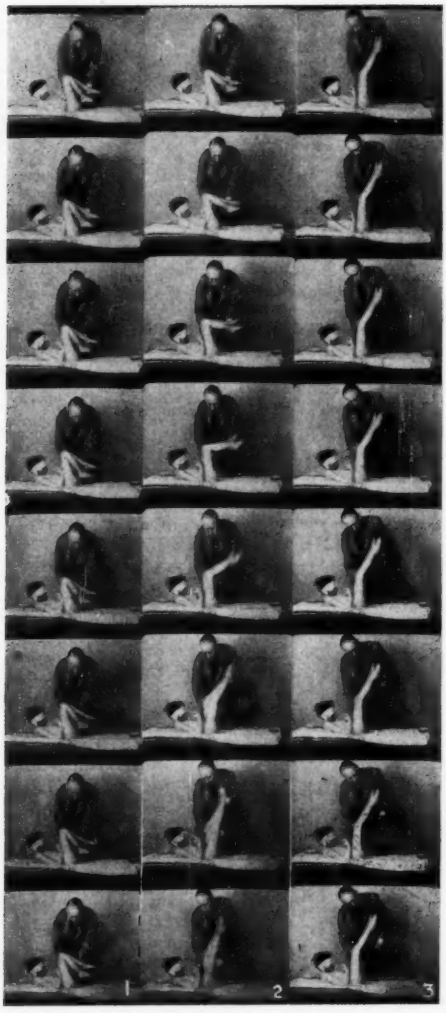

FIG. 3.—(1) Another idiot child in supine position. Both legs are kept in the posture of flexion. (2-3) After passive extension of the knees the passively given posture is retained and the legs are held straight up in the air.

near the ankle, and bend the knee against the knee-extensor's contraction, he feels the opposition offered by the extensor give way almost abruptly at a certain pressure; the knee can then be flexed without opposition. On

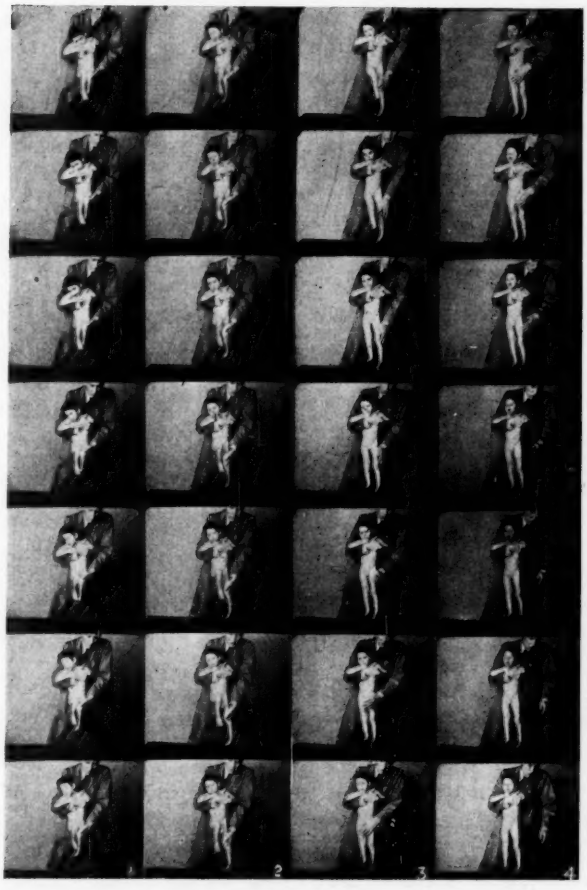

FIG. 4.—(1-2) The left leg is brought passively into the posture of extension. (3) This passive extension is followed by an active extension of the right limb. (4) Thereafter both legs remain in the posture of extension.

then releasing the ankle, the knee is seen to remain flexed approximately in that degree of flexion to which it had been carried by the manipulation."

This reaction, which was termed for brevity "lengthening reaction" is regularly accompanied by an extension of the crossed knee. The lengthening reaction too is specially marked in the decerebrate animal. "Starting with the knee in a posture of extension, due to its extensor's rigidity, the

observer forces it into flexion. On cessation of the flexing force the knee is found to remain approximately in the new posture. If the degree of flexion to which it has been subjected be but partial, the knee remains flexed partially. If then forced to full flexion it remains flexed more fully." For instance, if the knee is flexed from an initial angle of about 120 degrees to an angle of about 60 degrees, it remains on release at an angle of about 65 degrees.

In the chronic spinal animal the lengthening reaction cannot be so perfectly graded as in the decerebrate animal. In spinal animals it is easy to change the posture of the knee from one of tonic extension to one of flexion, but it cannot so easily be made to retain intermediate postures.

The lengthening reaction is also obtainable in the "isolated vastocrureus preparation." The isolated vastocrureus of the decerebrate animal, when subjected to a stretch, remains after the application of the stretching force has ceased at a new and increased length. Sherrington has suggested that "the enduring elongated state produced in the tonic muscle by the forced stretch may be due to reflex-inhibition of the tonus of the motoneurones supplying the muscle." After the cessation of the stretching force, however, the muscle bears again its load, that is to say the limb below the knee. If, the animal being supine, the knee is passively bent from full extension to an angle, whereby the limb below the knee is almost horizontal, then after the cessation of the passive stretch the elongated vastocrureus has, due to the greater level, to bear a heavier load than in the primary posture of full extension, and still the elongated length is retained. In these circumstances the vastocrureus has, after the cessation of the passive stretch, not a smaller, but a greater, tension than previous to the stretch.

There, again, the vastocrureus does not "know" the weight of the load which it has to bear after the release of the limb, it is evident that also in the lengthening reaction the tension of the vastocrureus, after the release of the limb, must be determined by the weight of the load or, in other words, by the stretch reflex. It results from these facts, that the tension in the elongated length is not due to reflex-inhibition, but to a reflex-contraction. Furthermore, it has been observed by Sherrington that if the knee is flexed from an initial angle of about 120 degrees to an angle of about 60 degrees, it remains on release at an angle of about 65 degrees. Thus the vastocrureus raises the load before it retains its new elongated length. And also in the graphic records (fig. 5), published by Sherrington, it can be noted that the load is first raised (and thereafter drops) before the muscle remains at its new length. This demonstrates

that, at the moment of the release of the limb, the tension of the vastocrureus is greater than the weight of the load!

Samojloff and Kisseleff, in repeating the experiments of Sherrington, have simultaneously registered the action currents of the vastocrureus, and they have thereby observed that during the passive bending of the knee the action currents do not diminish, but increase in strength. Immediately after the release of the limb, however, the action currents abruptly decrease. This decrease, which occurs during the raising of the limb, is succeeded by a reappearance or increase of the action currents, occurring simultaneously with the dropping of the limb. Thereafter, during the maintenance of the new length small action currents persist. It is obvious from these observations that the mechanism of the lengthening reaction is as follows: The passive bending of the knee elicits the

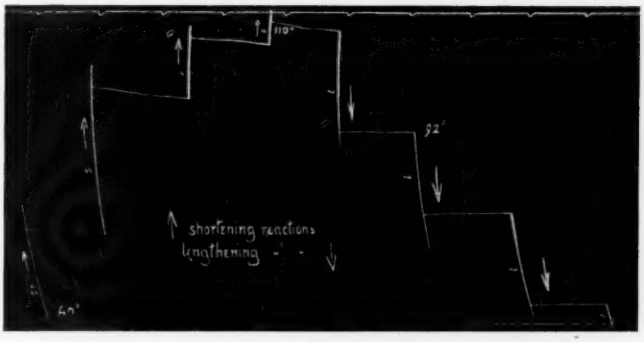

FIG. 5.—Lengthening and shortening reaction of the isolated vastocrureus of a decerebrate cat (Sherrington, *Quart. Journ. Exper. Physiol.*, **2**, 118, 1909).

stretch reflex, so that the tension of the vastocrureus increases. By the heightened tension the limb below the knee is raised as soon as it is released, and the vastocrureus contracts and is shortened. This shortening of the vastocrureus produces a diminution or abolition of the stretch reflex, so that the muscle relaxes, the raising of the limb is checked, and the latter drops instead of being further raised. By the dropping of the limb the vastocrureus is passively lengthened, so that the stretch reflex comes once more into play, with the result that the fall of the limb in its turn is checked and so the vastocrureus retains its elongated length.

In the initiation of the lengthening reactions there is thus the following succession: (1) The stretch reflex excited by the passive bending of the knee; (2) the diminution or abolition of the stretch reflex evoked by

the shortening of the vastocrureus after the release of the limb; (3) the stretch reflex elicited by the succeeding drop of the limb.

The lengthening reaction, like the shortening reaction, can also be observed in man (figs. 6 and 7).

In order to be obtained, it is necessary that the reactions are released from cerebral control. If this condition is fulfilled the examination of the subject does not entail a cerebral inhibition of its reactions, and,

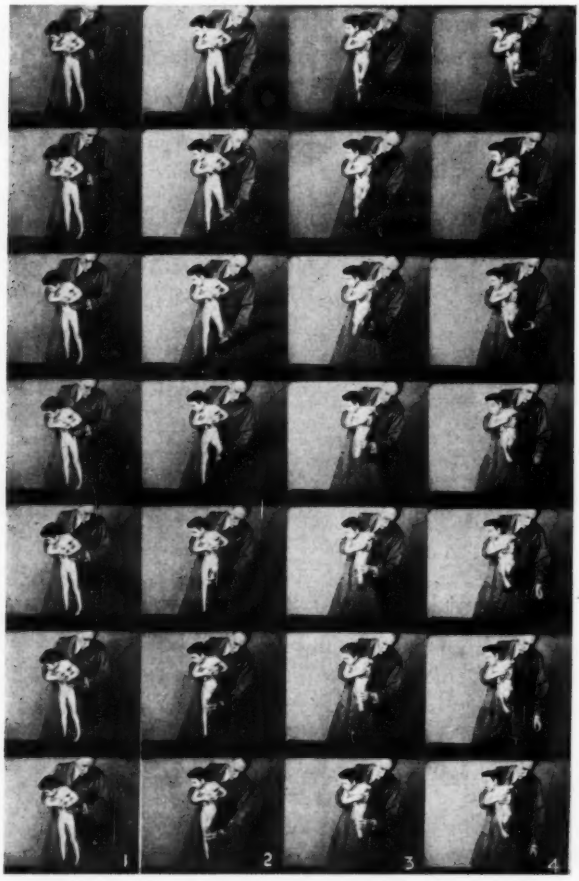

FIG. 6.—(1) An idiot child, kept upright in the air by holding it under the shoulders. Its legs are stiff and are kept in the posture of extension. (2-4) After passive bending of the knees the posture of flexion is retained.

FIG. 7.—(1) The same child, being supine, holding both legs rigidly in the posture of full extension. After passive bending of the left leg the right one remains extended. (2-3) After passive bending of both legs the posture of flexion is retained.

moreover, only when this condition is fulfilled, it is certain that the occurring reactions are reflexly, and not voluntarily, brought about. It is, therefore, that the lengthening and shortening reactions can best be studied in children with marked idiocy.

Both reactions being accomplished by the action of the stretch reflex a second essential condition for their occurrence is that this reflex is easily excitable, and that the sensory end-organs which initiate the impulses evoking the stretch reflex and the reflex-path of these impulses are intact. It is for this reason that both reactions are easily obtainable in cases of idiocy accompanied by slight or moderate rigidity and easily excitable knee-jerks and other tendon-reflexes.

The third essential condition is the prompt occurrence of the decrease or abolition of the stretch reflex when the knee-extensor is shortened, either passively or by the tension produced by the stretch reflex. If this decrease does not occur or if its influence is not strong enough to abolish the increase of the tension produced by the passive bending of the knee, then the lengthening reaction is not obtainable, and on being released after the passive bending of the knee the limb springs back to its original extended posture. This is to be observed in cases with extreme extensor-rigidity of the legs.

The lengthening and shortening reactions can also be obtained in cases of disseminated sclerosis, with so marked paralysis of the legs that they cannot voluntarily be moved and are practically released from cerebral control. The rigidity of the legs, however, may not be so extreme that it is impossible to bend the knee passively, or that the leg, on being released, after the bending of the knee, springs back immediately into the previous posture of extension.

By means of the lengthening and shortening reactions it is reflexly brought about that a muscle can bear different loads at different lengths, also at a few shortened and a few elongated lengths. In between the capacities to bear different loads by a few shortened and by a few elongated lengths there is its capacity to bear different loads by the same length.

It is obvious that there are gradual transitions between these reactions which seem, at first sight, so entirely different, but which have all the same purpose (aim): to keep unaltered the length of the muscle. It is, therefore, not so astonishing, that the three functions, the capacities to bear different loads by a shortened, by the same, and by an elongated length, are brought about by the same mechanism, that is to say, by the stretch reflex, which prevents the passive lengthening of the muscle by the load, in combination with the disappearance of the stretch reflex

elicited by the approximation of the end-points of the muscle, which prevents its shortening and checks the raising of the load by the stretch reflex. It is due to this combination that a muscle can reflexly bear the same and different loads by its various lengths.

The Clasp-Knife Phenomenon.

In 1909 Sherrington has given the following definitions of the two above-mentioned reactions: "The lengthening reaction is as follows: When the tonic muscle is stretched it assumes, by virtue of its proprioceptive arc, a new tonic length which is approximately that to which it has been stretched. Conversely, when in the tonic preparation of the knee-extensor the muscle is shortened, either passively or by active contraction of the muscle itself, the muscle retains approximately the shortened length thus given it. This is the shortening reaction."

In 1924 Sherrington and Liddell published their researches on the stretch reflex, which evidently proved that a passive elongation produces, instead of a reflex-inhibition, a reflex-contraction of the lengthened muscle. Thereafter, in a monograph on the reflex activity of the spinal cord, published in 1932 by Sherrington and his collaborators Creed, Denny-Brown, Eccles and Liddell, the following, somewhat different, definition of the lengthening reaction was given: "If an attempt be made to bend the knee or ankle of a decerebrate animal or of an animal with an isolated spinal cord (chronic spinal animal), one's hand meets resistance from these muscles which extend the joint. The attempt is, in fact, causing a further accentuation of the stretch reflex in muscles which are already highly responsive to stretching. If the attempt to flex the joint is maintained, there comes a point and time at which the muscle suddenly gives way and allows any degree of flexion to be imposed on it (clasp-knife effect). This is the lengthening reaction, and it marks the partial or total abolition of the stretch reflex."

In the first definition of the lengthening reaction stress is laid upon the retaining by the knee-extensor of the passively induced greater length, whereas in the second definition the sudden decrease of the resistance offered by the knee-extensor is stressed. The two phenomena, the retaining of the passively given greater length and the abrupt lessening of the resistance against passive stretch (clasp-knife effect) are considered by Sherrington as being parts of one and the same reaction, the lengthening reaction.

This view may be exact, its exactness is, however, not yet proved; in other words it is not established that the retaining of the elongated length

by the knee-extensor necessitates a previous abrupt vanishing of its tension during the passive bending of the knee. For this reason the two phenomena, the retaining of the passively induced elongated length by the knee-extensor (lengthening reaction) and the abrupt lessening of its tension (clasp-knife effect) are considered separately. In their researches on the mechanism of the lengthening reaction Samojloff and Kisseleff observed that the action currents of the knee-extensor did not decrease, but always increased, during the passive bending of the knee. Nevertheless, the abrupt vanishing of the resistance against the passive bending of the knee can often be felt quite distinctly. In the fore-limb the clasp-knife effect is frequently still more marked than in the hind-limb, especially when the elbow is passively flexed by exerting pressure against the pads of the toes. Sometimes it can thereby be observed that the resistance vanishes, although the action currents of the triceps do not disappear nor decrease. The mechanism of the subsiding of the resistance is then quite obscure.

Sherrington has suggested that the clasp-knife effect is due to the following course of events. If a muscle is stretched the centres receive excitatory impulses from the tension receptors and they respond by evoking the stretch reflex. During the stretch reflex, however, certain other end-organs send inhibitory impulses to the centres, but they are relatively infrequent, in contrast to the excitatory. The excitatory state of the centres, therefore, is not diminished perceptibly until a stage when the tension is considerable and possibly dangerous. At that stage the inhibitory impulses gain ascendancy and the muscle relaxes.

It is certainly true that by stretching a muscle forcibly more and more a stage is reached, by which the reflex-tension and also its action currents disappear. The clasp-knife effect, however, often already occurs, when the bending force is not at all exaggerated, but only moderately strong. It is obvious that with regard to the mechanism of this effect much is still in the dark.

If in the cat the knee is bent from full extension to full flexion the quadriceps is lengthened for about 24 mm. As was mentioned above, it has been observed by Sherrington and Liddell that in the decerebrate cat a stretch of less than 1 mm. of the quadriceps may give a contraction developing more than 2 kg. tension, and furthermore that the greater the passive stretch the greater is the reflexly elicited tension. These observations may lead to the conclusion that in decerebrate cats bending of the knee is practically impossible, and that it necessitates a force far greater than 2 kg. Everyone, who has performed experiences on decerebrate cats, has noted that sometimes, when the decerebrate rigidity is unusually intense, a really very strong force must be exertised, but mostly such an excessive force is not at all necessary. Not in every decerebrate cat does the knee-extensor respond

on a stretch of 1 mm. with a contraction of 2 kg. tension. In order to obtain such a strong tension the extensor must often be stretched several (4 or more) mm. Furthermore, when the attempt to bend the knee is maintained, the resistance offered by the knee-extensor diminishes gradually, so that after a certain lapse of time the knee can be brought into flexion by a moderate force. It has been observed by Sherrington and Liddell that if the knee-extensor is subjected to an extension of 3 mm. the stretch reflex so elicited may maintain itself for half an hour or longer, but if the extension is 7 mm. the stretch reflex subsides in five or ten minutes; thus the greater the passive stretch the sooner the stretch reflex subsides and the resistance diminishes. Sherrington and Liddell have suggested that this subsidence of the stretch reflex is due to the cumulative effect of inhibitory impulses which, besides the excitatory impulses provided by special end-organs,

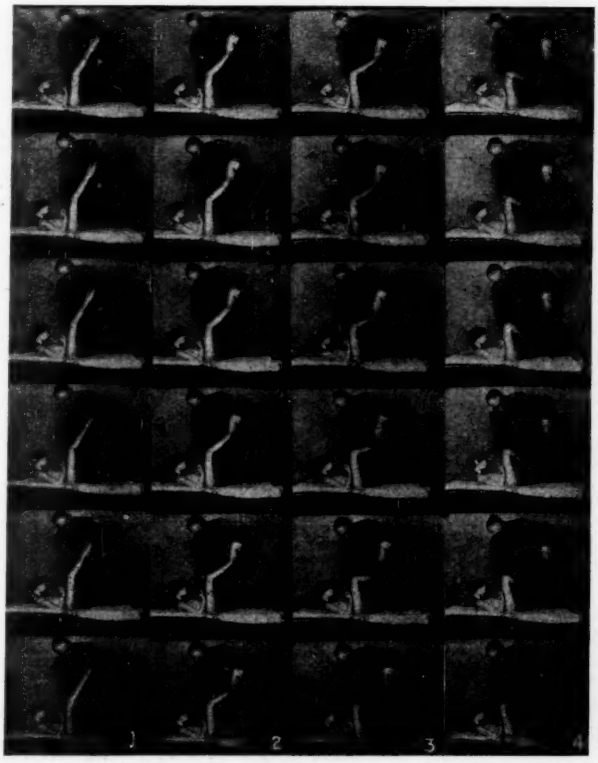

FIG. 8.—(1) Idiot child supine. After the passive extension of the knees the posture of extension is retained and both legs are held straight up in the air. (2) The knee of the *right* leg is passively slightly bended. (3) This produces first a drop of the *left* leg below the knee, and thereafter, the right one being released, also of this leg. (4) Finally both legs drop till a full flexion of the knees is reached.

are sent by other end-organs in the muscle to the centres of the stretch reflex. Presumably it is owing to this subsidence that a prolonged passive stretch produces, as a rule, a more complete lengthening reaction than does a briefer though otherwise similar passive stretch, and it seems likely that this subsidence plays a part also in the initiation of the clasp-knife phenomenon.

The clasp-knife phenomenon too can often be observed in those idiot children, which manifest the lengthening and shortening reactions. It can be elicited in these children as follows. The child supine, the hips are first passively flexed and then the knees passively extended. Due to the shortening reaction of the knee-extensors this posture is maintained after the release of the limbs, so that these are held straight upwards in the air. If, then, by moving the tibial part of one of the legs downwards, the knee is passively slightly flexed, it is often felt that the resistance subsides, and if the limb is then released it drops till full flexion is reached (fig. 8). A slight pressure on the tibial side of the limb is often already sufficient to evoke the subsidence of the tension of the quadriceps and to initiate the drop of the limb, which is not checked by the stretch reflex, but is going on till the posture of full flexion is obtained.

This reaction is often accompanied by the dropping of the crossed limb, thus by a crossed flexion (fig. 8).

It appears therefore that the slight pressure on the tibial side of the limb entails in this case not only an inhibition of the tension of the homolateral quadriceps, but also of the crossed knee-extensor, and furthermore an inhibition on both sides of the stretch reflexes during the dropping of the limbs.

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THE ORGANIZATION OF THE MOTOR CORTEX OF THE MONKEY BASED ON ELECTROMYOGRAPHIC STUDIES.

BY

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By the use of condenser discharges applied to the motor cortex of rabbit, cat and monkey (*Macacus rhesus*) for several seconds, Murphy and Gellhorn (1945) showed that the motor effect was not restricted to single muscles but evoked contractions of several muscles within the large somatotopic divisions of the body (arm, leg, face). Moreover, it was found that there was a central overlap in the cortex which applied even to muscles belonging to different somatotopic areas. Thus it was shown that cortical stimulation for five to ten seconds with stimuli at slightly supra-threshold intensities caused a contraction in hind- and fore-leg muscles or in muscles of fore-leg and face at the same time, the foci for the former being located more medially and for the latter effect situated more laterally on the lateral surface of the motor area. The degree of overlap seemed to decrease from the rabbit's brain to that of the cat and was least in the monkey; however, all experiments showed that several muscles were represented in small cortical foci. These observations were confirmed in experiments in which small cortical areas were surgically isolated. On the basis of these data, which appear to be in accord with the clinical observations of Hughlings Jackson, and the critical evaluation of the literature by Walshe (1942), it was concluded that: "The motor cortex does not consist of a great number of mutually exclusive and independently operated 'tiles' of grey matter, the whole forming a mosaic of individual muscular representation, but is, rather, a multipotential organ in which movements of different parts of the somatic musculature are broadly, although not co-extensively, represented. The cortex of the brain is a tissue physiological assay of any single part of which will reveal multipotentiality, but to a degree varying according to the part selected for examination and dependent on the species chosen" (Murphy and Gellhorn, 1945).

Whereas in the study of Murphy and Gellhorn the conclusions were

[1] Aided by a grant from the National Foundation for Infantile Paralysis.

based solely on the observation of the movement, it was attempted in the present investigation to contribute further to the understanding of the multiple representation of cortical motor functions by recording objectively the movements through electromyograms. This method, allowing one to study the time relations and the degrees of activity of various muscles involved in a single movement in a more detailed fashion than is possible by a simple observation, avoids the pitfalls incident to isolation of the muscles and graphic recordings of their tension (cf. Tilney and Pike, 1925).

Methods and material.—The experiments were performed on fourteen monkeys anæsthetized with ·33 to ·50 c.c. of Dial-Urethane (Ciba)[1] per kg., i.p. The motor cortex was stimulated with condenser discharges at a frequency of 90/sec. for ten seconds as previously reported from this laboratory (Murphy and Gellhorn). Succeeding stimuli of threshold and suprathreshold intensities were separated by

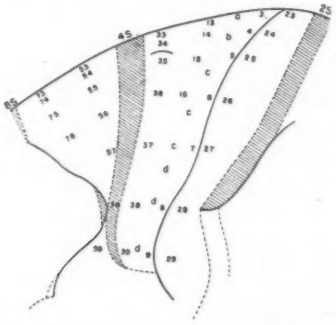

FIG. 1.—Diagram of cortical areas stimulated.

intervals of two to five minutes. The responses principally used for study were those resulting from stimuli slightly above the threshold, which caused movements resembling voluntary function. The sites stimulated are shown in fig. 1.[2]

Close observation of the movements of the animal was supplemented with electromyographic tracings[3] obtained from fine-wire electrodes sewn into the muscles. The muscles used were the biceps and triceps (fourteen monkeys), hamstrings (semitendinosus-semimembranosus) and quadriceps femoris (six monkeys), flexor and extensor carpi radialis (ten monkeys). The flexor and extensor carpi ulnaris were used in two monkeys, in one of which they were compared with the flexor and extensor carpi radialis and found to respond in a similar though not identical manner. The selected muscles were identified by direct stimulation through the paired electrodes and frequently at autopsy.

[1] Kindly supplied by the Ciba Pharmaceutical Company.

[2] Intermediary points such as a point between 5 and 6 are indicated in the legends by 5-6.

[3] All figures read from left to right.

Results.—Electromyography was found to be a valuable method for the study of motor activity, not only because it provides an objective record of the response but also because this method is far more sensitive than observation by other means. This applies particularly to the triceps and the carpal muscles, the activity of which is revealed far more clearly by the E.M.G. than by overt movement. Multiple recording also has enabled us to detect patterns and sequences within several muscles of the individual limbs or in combinations of limbs. In several instances, these patterns or sequences were originally observed in the E.M.G. and, with this key, their apparent motor equivalents were first detected.

Progression from the hind-limb to fore-limb movements was found, in agreement with previous investigators, as the electrodes were moved from medial to lateral sites in area 4 of the cortex. The movements of the hind-limb consisted almost exclusively of flexion of the hip and knee and

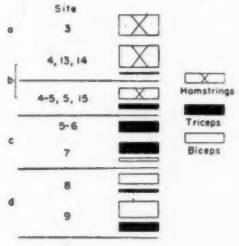

FIG. 2.—Schematic representation of the activity of hamstrings, triceps and biceps muscles as produced by electrical stimulation of different cortical sites.

dorsal flexion of the foot. The movements observed in the fore-limb may be divided into two groups, those involving retraction of the shoulder and extension of the elbow, and those consisting of protraction of the shoulder and flexion of the elbow with or without clenching of the fist.

The first type of movement of the fore-limb was associated frequently with flexion of the hind-limb, particularly on stimulation of the more medial areas of its response. The resultant motion is part of the natural gait, since it involves a movement of the fore-leg similar to that of the supporting phase and, at the same time, a flexion of the hind-leg. Responses from stimulation in the more lateral part of the cortex from which this type of movement could be elicited caused an associated flexion of the wrist. Though this movement was often barely discernible visually, it was manifested clearly in the electromyogram of the response in the flexor carpi muscle.

The second type of movement, resembling prehension, was seen on stimulation of lateral areas of the motor cortex. As the electrodes were moved still farther laterally, this movement occurred with a response in the facial muscles.

The diagrams of fig. 2 indicate the topographic distribution of these movements as they were disclosed in an actual experiment in which electromyograms of the quadriceps, the hamstrings, the biceps and triceps muscles were recorded. If we divide the lateral surface of area 4 for purposes of description, into four zones of approximately equal width (cf. fig. 1), it may be said that from the most medial zone (a) hind-leg flexion is elicited without admixture of contraction in fore-limb muscles. In these experiments, action potentials appear in the hamstring muscles but are in general not accompanied by activity of the quadriceps.[1] However, in the zone adjacent laterally (b), the flexion of the hind-limb indicated by the E.M.G. of the hamstring muscles appears in conjunction with a movement of the fore-leg involving shoulder muscles and triceps. Contraction of the triceps as indicated by the E.M.G. may be simultaneous with that of the hamstring group, or activity in either of these muscles may precede that in the other. This zone corresponds to the areas of central overlap of the fore- and hind-leg representation previously described by Murphy and Gellhorn. The electromyographic experiments add to their findings the significant fact that the movement elicited from this zone follows a definite pattern inasmuch as flexion of the hind-leg is associated with retraction of the shoulder and extension of the elbow.

Passing on farther laterally (zone c) it is noted that now only the forearm movement appears. In the more medial aspects of this area, potentials are seen in the triceps without co-activity in the biceps muscle, whereas, in the lateral part of this zone, biceps activity is accompanied by that of the triceps during extension of the elbow. Finally, in the most lateral zone (*d*) of area 4 biceps activity accompanying flexion of the elbow becomes increasingly prominent. It is associated with co-activity in the triceps muscle which occasionally appears at the height of the activity of the agonist only, but frequently is simultaneous with the total contraction time of the latter. Considering the biceps—triceps relationship on the basis of experiments performed on the zones c and d of area 4, it may be said that the flexion of the elbow is commonly accompanied by co-activity of the triceps (co-innervation) even in experiments which are performed at or very close to the threshold. However, extension of the elbow

[1] A more detailed study of the hind-leg movements and of the factors leading to a greater activation of the quadriceps will be reported in a subsequent investigation.

elicited from the medial part of zone c may appear without co-innervation in the biceps. There is, in general, a greater tendency to co-innervation in movements of flexion than of extension of the elbow.

Fig. 3 illustrates diagrammatically the effect of cortical stimulation of zone b to d on biceps, triceps and carpal muscles. In the lateral part of zone b and the medial part of zone c, the previously described triceps activity occurring with retraction of the shoulder and slight extension of the elbow is associated with activity of the flexor carpi radialis and ulnaris. The triceps—flexor carpi pattern is fundamentally different from that elicited from the lateral part of area 4 (zone d) in which biceps activity is found to be associated with that of the extensor carpi radialis. If the intensity of stimulation is but slightly increased potentials appear also in

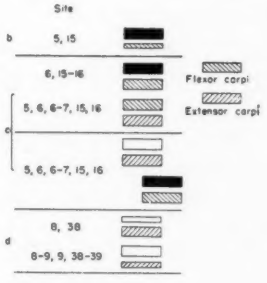

FIG. 3.—Schematic representation of the activity of biceps, triceps, flexor carpi and extensor carpi muscles.

the flexor carpi and this marked simultaneous activity of extensor and flexor of the wrist is accompanied by clenching of the fist.

It appears from these observations that the tendency to co-innervation of the antagonist which is found in the flexion of the elbow is present also in the commonly coincident action of the extension of the wrist[1] since activity in biceps and extensor carpi causes the appearance of distinct co-activity in triceps and flexor carpi whereas the triceps—flexor carpi pattern shows little or no co-innervation of the biceps and extensor carpi muscles.

When stimuli at or near the threshold are applied to those areas from which the biceps—extensor carpi and the triceps—flexor carpi patterns respectively are elicited, the motor response is not uniform but shows

[1] The latter phenomenon is shown by the appearance of activity in the flexor carpi at the time of strong contraction of the extensor carpi.

slight topographical differences. Under these conditions the medial part of the biceps—extensor carpi area elicits predominantly a response in the extensor carpi while activity in the biceps muscle is either absent or appears with a longer "latent period" than is observed in the E.M.G. of the extensor carpi. The opposite behaviour (weak or delayed response in the extensor carpi associated with strong activity in the biceps) characterizes the response from the lateral part of the biceps—extensor area. Similar distinctions are found in the triceps—flexor carpi area, the former component being more predominant in the medial, the latter more in the lateral parts of that area. Consequently, at or near the border between the zone eliciting the triceps and biceps complex respectively, an area may be found where at threshold stimulation only the carpal muscles respond. The relative prominence of activity in the carpal muscles was greater in some animals than in others.

There was little variation in the delimitation of the foci in area 4 from which the various patterns of motor response could be elicited. However, it may be mentioned that the relative amplitude of the E.M.G. of the wrist muscles as compared with that of the biceps and triceps showed considerable individual variations inasmuch as in some instances the amplitude was greater in the proximal than in the distal muscles, whereas in others the reverse was true. This description applies particularly to the central zones of area 4 and is valid only for foci from which simultaneous activity in proximal and distal arm muscles can be obtained.

From the central zone of area 4 a biphasic response was recorded. In the medial part of this "reversal" zone the first phase consisted of the extension and the second of the flexion of the elbow. The latter may occur with or without the making of a fist. The initial phase of the sequence was usually represented by both triceps and flexor carpi although, occasionally, activity was recorded only in one of the two muscles. In the lateral border of this "reversal" zone stimuli elicited activity in the biceps—extensor carpi complex only, whereas with stronger stimuli a biphasic response appeared in which the triceps complex represented the second phase.

The electromyographic records do not always show a sharp division between the two phases which have just been described. This holds true particularly under conditions resulting from stimuli of intermediate intensity when during the second phase of the "reversal" sequence (biceps—extensor carpi) activity may appear in the flexor carpi as a result of coinnervation. A separation between the two phases of the reversal response is sometimes indicated by a brief period of inhibition.

It was mentioned previously that as we proceed from the medial to lateral sites in the motor cortex, the electromyographic response passes through the following phases indicating contraction of the following muscles: (1) Hamstrings; (2) hamstrings + triceps + flexor carpi; (3) triceps + flexor carpi; (4) triceps + flexor carpi followed by biceps + extensor carpi; (5) biceps + extensor carpi; (6) biceps.

Although this sequence holds true for area 4 and apparently also for the adjacent parts of areas 6 and 3, 1, 2, closer study reveals that points yielding similar motor responses are not located on lines parallel with the sagittal plane even within area 4. Instead, foci of similar functional significance run from a medial anterior point to a more laterally located posterior site as indicated in fig. 4.

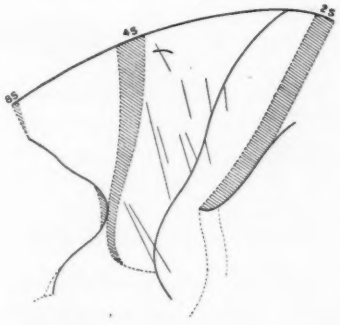

FIG. 4.—Diagrammatic representation of sites of similar function. Such sites are joined by lines which form similar angles with the sagittal plane.

A few typical examples may illustrate the innervation patterns resulting from stimulation of different foci on the lateral surface of the motor cortex. Fig. 5 shows examples of E.M.G. obtained from the same monkey. At the medial site 4 the motor effect is accompanied by large potentials in the triceps and small electrical variations in the flexor carpi radialis while the biceps and the extensor carpi radialis remain silent. The threshold was 4 v. at this point and the record of fig. 5*a* was obtained with a stimulus of 4·8 v. However, even an increase in stimulus intensity to 5·5 v. did not alter the movement pattern (extension of the elbow) or the electromyographic response. Passing to site 5-6 it is found that now the threshold is definitely lower for the distal than for the proximal muscles of the fore-arm. At 4 v. (fig. 5*b*) there is a distinct reaction in the extensor carpi radialis accompanied by a weak response in the flexor carpi

radialis while the records of the biceps and triceps muscles are silent. As we progress farther laterally to site 6 (fig. 5*c*) the biceps response appears even at a very low voltage although it is still very weak as compared to the activity in the extensor carpi muscles. A similar response obtains at the slightly more lateral site 7 (fig. 5*d*). However, an indication that the main focus of the biceps complex is approached is indicated by the low threshold (1·9 v. were used in the experiment of fig. 5*d*), and by the fact that now a distinct after-discharge appears in the biceps record which was

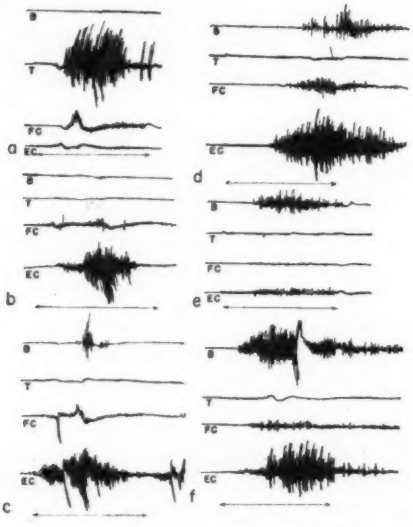

FIG. 5.—B = biceps; T = triceps; FC = flexor carpi radialis; EC = extensor carpi radialis. Arrow indicates duration of stimulation at cortical sites: a: 4·8 v. at site 4; b: 4 v. at site 5-6; c: 3·3 v. at site 6; d: 1·9 v. at site 7; e: 2·9 v. at site 8; f: 3·3 v. at site 8.

absent at more medially located sites (cf. fig. 5*c*). At site 8 (fig. 5*e* and *f*) a further strengthening of the biceps response has taken place since the electromyographic response is now stronger in the biceps than in the extensor carpi radialis. At low intensities the reaction is confined to the biceps—extensor carpi group, whereas at higher intensities of stimulation a response appears simultaneously in the flexor carpi although to a lesser extent than in the extensors of the wrist (fig. 5*f*). At the same time a clenching of the fist is seen.

All experiments have the fact in common that the lateral areas of the cortex elicit the typical biceps complex (biceps—extensor carpi muscles). The co-innervation of the triceps which appears while the elbow is flexed as well as the activity of the flexor carpi is somewhat variable in different animals and at different intensities. Fig. 6 shows in one animal a strong biceps—extensor carpi response at 3·3 v. with no activity in the triceps and flexor carpi whereas fig. 7 shows as the result of stimulation of a lateral prehension site activity in the proximal flexor and extensors. However, a glance at fig. 7 makes it obvious that the biceps—extensor carpi complex is predominant. Just as triceps activity appears with strong activation of

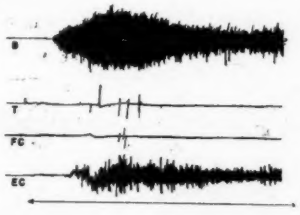

FIG. 6.—Symbols as in fig. 5. Cortical stimulation at site 8 with 3·3 v.

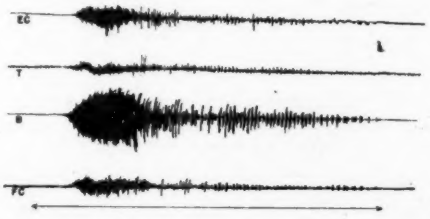

FIG. 7.—Symbols as in fig. 5. Cortical stimulation at site 9 with 3·1 v.

the biceps in flexion of the elbow (co-innervation, cf. Bosma and Gellhorn, 1946), so are action potentials seen in the flexor carpi in association with strong action of the extensors of the wrist. This co-innervation has the obvious function of stabilization of elbow and wrist joints.

The examples given in the preceding paragraphs have illustrated the fact that the medial sections of the motor cortex give rise to the triceps complex and the lateral foci to the biceps complex including the activity of the flexor carpi which contribute to the fixation of the wrist in grasping. Intermediate between these two areas is a zone with relatively low thres-

hold of the muscles activating the wrist. That, as was mentioned above, the medial part of the triceps area gives rise at the same time to a flexion of the hind-leg is illustrated in fig. 8. In this record the effect of two stimulations of slightly different intensities was recorded. In each instance a marked triceps response was associated with an activity in the hamstring muscles while the record of the biceps remained silent. It is seen, furthermore, that the triceps—hamstrings complex is preceded by that of the quadriceps. This phenomenon is seen but rarely in the suspended animal but was quite distinct in a monkey kept in a lateral position on the table. There seems to be partial reciprocity between hamstrings and quadriceps (fig. 8*b*) during and after stimulation. This reciprocity is most prominent in fig. 8*a* at the end of the stimulation period, as the activity of the ham-

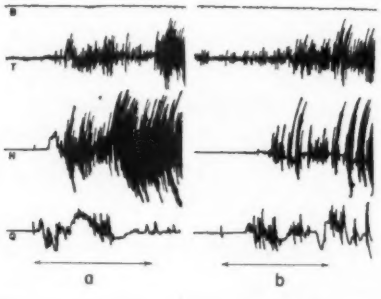

FIG. 8.—B = biceps; T = triceps; H = hamstring; Q = quadriceps femoris. a: cortical stimulation at site 3-13 with 3·3 v.; b: with 2·9 v.

strings increases and that of the quadriceps diminishes. There were suggestions in this as well as in other experiments of some reciprocity between triceps and hamstrings inasmuch as increase in hamstring activity was associated with decrease in triceps activity (cf. fig. 8*a* during the last third of the period of stimulation) and vice versa but simultaneous activity in triceps and hamstrings was commonly seen on stimulation of medial sites of area 4.[1]

The last phenomenon which we wish to demonstrate is a phenomenon of "reversal" which is obtained from intermediate zones of area 4 and consists of a retraction of shoulder plus extension of elbow followed by flexion of elbow and clenching of fist while the shoulder is protracted. The analysis of this complex movement has been accomplished only in some

[1] Further analysis of the hind-leg movement will be given in another paper.

of its important constituents, since the electrical activity of only four muscles could be recorded simultaneously.

Fig. 9*a* shows that initially on stimulation distinct activity is recorded

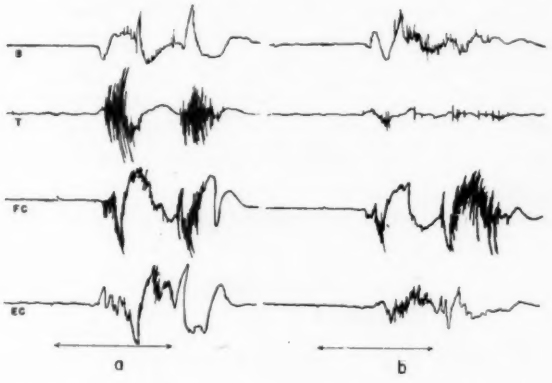

FIG. 9.—Symbols as in fig. 5. Cortical stimulation at site 7-37. a: 3·5 v. and b: 3·9 v.

in the triceps—flexor carpi muscles with no or minimal activity in the muscles of the biceps complex. However, as the stimulation continues, the activity of the triceps is completely inhibited and that of the flexor

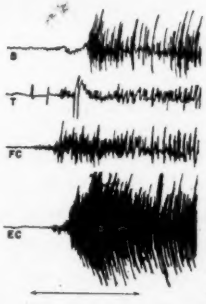

FIG. 10.—Symbols as in fig. 5. Cortical stimulation at site 5 with 6·3 v.

carpi radialis muscle is markedly reduced while activity in the biceps complex appears. A subsequent experiment performed a few minutes later with a slightly increased intensity of stimulation (fig. 9*b*) shows the

same pattern with a slight variation. The initial triceps response is weak; it is followed by a biceps response which appears together with that of the extensor carpi muscle while the muscles of the triceps complex are inhibited.

Fig. 10 shows an experiment in which the two phases of the reversal response are not too clearly separated but in which E.M.G.s appear first

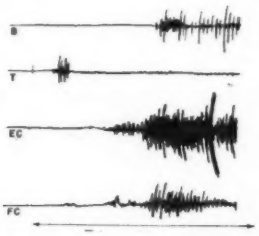

FIG. 11.—Symbols as in fig. 5. Cortical stimulation at site 13 with 10·8 v.

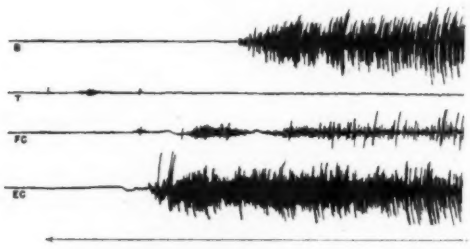

FIG. 12.—Symbols as in fig. 5. Cortical stimulation at site 14 with 9·5 v.

in the triceps—flexor carpi complex. A little later marked activity appears in the biceps complex while the activity in the triceps complex is greatly diminished. At sites medial to the reversal area the two phases of this movement complex are more sharply separated by relatively long periods of inhibition (fig. 11). At first appears a brief but distinct activity in triceps followed by a trace of activity in the flexor carpi. Then, after an inhibitory interval, activity is seen in the biceps complex and also in the flexor carpi which as was described earlier is associated with the movement of clenching a fist.

Fig. 12 shows a reversal experiment following prolonged stimulation of a rather medial cortical site in which the triceps—flexor carpi response

is weak but appears distinctly before activity is seen in the other recorded muscles. It is followed by a vigorous activity in the biceps complex. Whereas activity of the triceps complex starts with the triceps that of the biceps complex begins with the distal muscles. Here again activity is seen in flexor and extensor carpi muscles which is associated with the fist movement. It is, however, worthy of note that with the initiation of the activity of the biceps there appears a period of inhibition in the flexor carpi muscle.

The following experiments seem to show more incomplete forms of the reversal phenomenon. On stimulation of site 5-6 (fig. 13*a*) at or near the threshold, activity appears solely in the flexor carpi radialis, whereas at higher intensity (fig. 13*b*) the biceps complex is also called forth. The E.M.G. of the flexor carpi radialis is not continuous as it was under con-

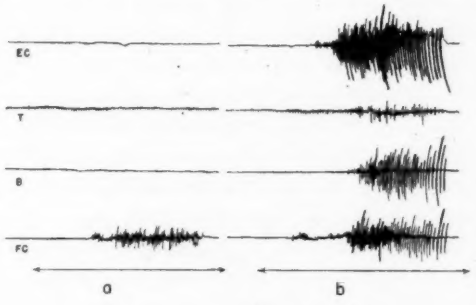

FIG. 13.—Symbols as in fig. 5. Cortical stimulation at site 5-6. a: 3·9 v. and b: 6·3 v.

ditions involving a lesser degree of stimulation and during the period of inhibition the extensor carpi contracts as part of the biceps complex. This experiment is a typical example of observations in which one of the phases of the bi-phasic response is incomplete. In this case the initial triceps response was completely absent whereas in other cases the flexor carpi remained silent. In the areas adjacent to the zone of "reversal" such rudimentary responses are found most frequently.

DISCUSSION.

The most important result of the investigation reported in this paper is the confirmation and implication of the principle of multiplicity of muscular representation as established experimentally by the earlier studies of Murphy and Gellhorn. Since the method was the same in both

investigations and a large part of the significant experimental results was obtained with slightly suprathreshold stimulation, i.e. with lesser intensities than were used in the previous work, the arguments and experiments presented by Murphy and Gellhorn which seem to exclude physiological and physical cortical spread are applicable to the present investigation. The simultaneous recording of activity of the hamstring muscles with that of the triceps gives objective evidence of the overlap existing between the cortical representation of large somatotopic areas such as hind- and fore-leg. That a considerable number of muscles of one extremity is activated from a single cortical focus was recorded in numerous experiments by electromyograms. These records showed that during stimulation the movers of the elbow and wrist were activated. Numerous other muscles were involved in the movements although, owing to the limitations of the apparatus, not more than four muscles could be recorded simultaneously. The inclusion of muscles of the shoulder and of the fingers promises greatly to increase our knowledge of the organization of the motor cortex. However, the simultaneous recording of hind- and fore-leg muscles as well as that of upper arm and wrist muscles is adequate to refute the punctate theory as applied commonly to the motor cortex.[1]

It seems to follow from our results that the neurons representing individual muscles in the cortex are not confined to narrow, sharply circumscribed foci but correspond rather to bands which greatly overlap those of other muscles. Moreover, these bands are not uniform but show varying densities of specific neurons. This interpretation is suggested, to cite one example only, by the fact that proceeding from the intermediate to the lateral zone of area 4 slightly suprathreshold stimuli produce activity of the biceps to an increasing, and that of the extensors carpi to a decreasing, degree. Although differences in the threshold of specific motor neurons in different parts of the motor cortex may play a contributing role, the findings of similar results when stimuli of much greater intensity are applied suggests that the neurons are distributed unevenly, i.e. in the present example, that the number of biceps neurons increases with increasing laterality of the cortical focus whereas the reverse statement holds for the distribution of the neurons activating the extensors carpi radialis and ulnaris. These lesser concentrations of neurons are activated only under favourable conditions permitting facilitation and are, therefore, neglected when the cortex is stimulated for very brief periods.

[1] Concerning the discussion of the relevant literature cf. the paper of Murphy and Gellhorn.

A further assumption dealing with intracortical relations is necessary to account for the data described in this paper. The demonstrated fact that movements induced by electrical stimulation of the cortex are co-ordinated in time and space, suggests that the electrical stimulus elicits a process in the cortex through which the locally represented neurons are activated in certain patterns. The anatomical basis of muscular co-ordination is believed to lie, to a large extent, in the intracortical connections existing between neurons which, although supplying different muscles, are located in the same cortical focus. Were this not the case the various muscles would be activated in a strength commensurate with the number of neurons present but without the temporal sequence which is characteristic of movements induced by cortical stimulation as well as by volition.

Whereas the investigations of Murphy and Gellhorn were largely confined to the determination of the cortical foci of the muscles or groups of muscles which produced movements of the various joints of fore- and hind-leg and of the face, the present study made it possible, by the use of electromyograms, to ascertain their functional interrelation in at least a few instances. The most complex movement noted was the biphasic reaction elicited from the "reversal" area. Retraction of the shoulder with extension of the elbow was followed by protraction of the shoulder, flexion of the elbow and finally clenching of a fist. The temporal sequence, often clearly demarcated by periods of inhibition, permits one to recognize in this complex certain elements which are obtained outside of the reversal area. Thus the retraction of the shoulder and extension of the elbow is commonly combined with a flexion of the hind-leg in the more medially located parts of area 4 whereas the flexion of the elbow and the clenching of the fist is elicited from a zone of area 4 which is lateral to the reversal area. This relatively simple example shows one of the important principles of the organization of the motor cortex that not contractions of individual muscles but functionally significant movements form the elements of more complex movements. The great variety of movements resulting from cortical stimulation or voluntary action appears to be the result of numerous combinations of such functional elements. This interpretation is in agreement with the clinical experience that as a result of cortical lesions the activity of a certain muscle is lost in one form of movement while it may persist in a different movement which apparently involves another functional unit of which the muscle in question is a part. It will be the task of further experimental work to determine these functional units and their cortical representation. However, even if by a very detailed electromyographic study of many muscles the organization of

the motor cortex were much better known than it is at the present time an important gap in our knowledge would still exist since the modification of cortically induced movements by proprioceptive and other afferent influences was not taken into account.

Since some of the problems and results relative to the effect of afferent impulses on the motor cortex will be discussed in a following paper it may suffice to call attention only to the well-known fact that cortical stimulation results predominantly in flexor and not in extensor effects. The triceps activity was in most experiments weak and we failed often to record any activity in the quadriceps. The reason for this peculiar result is probably that the animals were suspended in a prone position with the extremities hanging freely downwards. Consequently, the flexor muscles were more stretched as a result of gravity than the extensors, and Magnus has shown clearly the fundamental influence of this stretch on the effect of reflex or cortical stimulation.[1] In view of the results reported in a following paper and other material which is still unpublished, it appears to be very probable that proprioceptive impulses have a profound effect on the co-ordination of movements elicited by stimulation of the motor cortex.

Summary.

Experiments were performed on monkeys in Dial-Urethane anæsthesia on the organization of the motor cortex. The lateral surface of area 4 and, to a lesser extent, that of the adjacent anterior and posterior cortical zones was stimulated with condenser discharges for ten seconds and the motor effect was recorded by four electromyograms of fore- and hind-leg. The results were as follows:—

(1) The central overlap between fore- and hind-leg muscles as well as between the muscles acting on the various joints of the fore-leg (cf. Murphy and Gellhorn, 1945) is confirmed by electromyographic records.

(2) Stimulation of a cortical focus results in definite patterns of movements. From the medial aspect of area 4 a progression pattern is elicited which is characterized by flexion of the hind-leg in conjunction with retraction of the shoulder, extension of the elbow and flexion of the wrist. From the lateral parts of the motor cortex a grasping pattern is evoked consisting of protraction of the shoulder, flexion of elbow and clenching of the fist. The intermediate part of area 4 (zone of reversal) gives rise to

[1] We have confirmed these results through electromyographic experiments as yet unpublished.

combination of parts of both responses since retraction of shoulder and extension of the elbow is followed by protraction of shoulder, flexion of elbow, fixation of wrist and clenching of fist.

(3) The functional units called into action by stimuli applied to the motor cortex in a medial-lateral progression are: (*a*) hamstrings—triceps complex; (*b*) the triceps—flexor carpi combination and (*c*) the biceps—extensor carpi group. The distribution of the neurons which activate a certain muscle or group of muscles does not seem to be uniform even within a certain focal area. This is suggested by the fact that the effect on the biceps increases relative to that on the extensor carpi as the stimulus passes to more lateral sites of the area from which the prehension pattern is elicited. Similar distinctions can be made for the individual components of the other two functional groups enumerated in this paragraph. The electromyographic records which furnish these data support the assumption that the cortical foci consist of bands in which certain specific neurons (e.g. those activating the biceps) are intermingled with those of other specific neurons (e.g. those innervating the extensor carpi muscles) which form the anatomical substrate of simple patterns of motion. The fundamental difference between these individual functional units is apparent from the electromyographic records inasmuch as there is a tendency for inhibitory phases to appear in one unit when activity begins in another unit. However, with increasing intensity of action co-contraction of such antagonistic muscles may occur. Such co-innervation of the triceps during the performance of a flexion of the elbow is more common than co-innervation of the biceps during cortically induced extension of this joint. Similarly it is seen that even strong activation of the flexor carpi (occurring commonly in conjunction with activity in the triceps) is but rarely accompanied by a co-contraction of the extensors of the wrist whereas activity of the extensors carpi (appearing as part of the biceps complex) is commonly associated with activity of the flexor carpi muscles (co-contraction). Apparently strong innervation of the biceps complex leads to a certain degree of fixation of elbow and wrist, the latter being an essential part in the effective clenching of the fist.

(4) Motor effects elicited from the adjacent parts of area 6 and from the anterior part of the post-central gyrus follow patterns similar to those described for area 4. Cortical points yielding similar motor actions are located on lines which are not parallel to the mid-line but connect medial anterior foci with slightly more laterally located posterior points.

(5) It is believed that stimulation of the motor cortex under conditions

permitting facilitation gives a more accurate picture of the distribution of neurons in this area than does brief threshold stimulation which led many authors to believe in the mosaic (punctate) hypothesis of cortical representation. But even the former conditions of the stimulation still give an incomplete account of the potentialities of the motor cortex since they neglect the important role of afferent (proprioceptive as well as nociceptive[1]) impulses. The significance of the latter will be shown in subsequent papers of this series.

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[1] cf. Thompson and Gellhorn.

ON THE PATHOGENESIS OF CAUSALGIA IN PERIPHERAL NERVE INJURIES.

BY

P. W. NATHAN.

CAUSALGIA is a pain described as burning, like fire, like a red hot wire. This pain is said by Weir Mitchell, Morehouse, and Keen (1864) to vary in intensity "from the most trivial burning to a state of torture." They introduced the term "causalgia" to describe a pain, and they referred frequently to "the type of pain called causalgia," or to "a constant causalgia or burning pain." It has become customary to use the term to describe only the most severe pain associated with various signs and symptoms occurring only in partial traumatic lesions of peripheral nerves; these many, and often incompatible, associations include arteriolar and capillary dilatation and constriction, hyper-, hypo- and anhydrosis, œdema, atrophy and glossiness of the skin, slow rate of growth of nails, and osteoporosis. It is clear that the term now means different things to different men; and that many attempt to account for the pain by considering some of its associations as its cause, although these associations are not always present. It is therefore desirable to stress the definition of Weir Mitchell (1872) —that causalgia is burning pain.

This pain, which is not always of great severity, is easily recognized from the spontaneous descriptions of the patients. Associated with it there may be anhydrosis or hyperhydrosis, dilatation of the capillaries and arterioles, cyanosis or redness of the skin, œdema, osteoporosis, anæsthesia or normal tactile sensibility, analgesia or hypoalgesia. These signs may occur with lesions of peripheral nerves without causalgia.

DESCRIPTIONS OF SOME SEVERE PAINS OF PATIENTS WITH PERIPHERAL NERVE INJURIES.

The subjects of peripheral nerve lesions have other pains besides causalgia, pains which may be more severe; with little distortion of their descriptions it is found that they complain of three types of pain: causalgia, pins and needles pain, and deep pain.

The descriptions of the pains of 10 patients with lesions of peripheral nerves causing causalgia are given below. A further 6 patients are in the series which was investigated; their descriptions are similar to those quoted, and are not given for the sake of brevity.

Case 1.—Lt. A. (Partial sciatic lesion.) The pain began as an irritation throughout the whole limb, and gradually became worse, so that he could not sleep. It consisted of burning, pins and needles, and aching; it felt as though the foot had been burnt. The pins and needles sensation came as a preliminary to the feeling of burning. The burning came on in surges, each surge lasting from 2 - 5 secs. and coming every 15 - 20 secs.; the burst of surges lasted from ½ to 2 hours, and came on every 1 to 1½ hours; but he was never entirely free from it. In addition, he had a soreness, a kind of aching in the heel, so that he had pain whenever his heel touched the blanket. This was improved by changing his position, although no one position was better than another. Cold water stopped the pain immediately and almost completely, but the pain became so severe on taking the limb out of the water that he considered this remedy useless. He would not let anyone touch the leg or foot, but would do so lightly himself, when requested to feel out the area of skin denervation. Further questioning on other occasions confirmed that the burning pain and pins and needles were different: he had the pins and needles most of the time, but the burning came on in surges, superimposed on the pins and needles; he stated that he could stand the pins and needles, but "the burning is hellish." Only the burning pain was kept away by the cold water; the pins and needles remained. The pain had originated fourteen days after wounding.

On examination it was found that there was hypoæsthesia in the sciatic distribution, and raised threshold to painful stimuli, with increased sensitivity when this threshold was passed. There was no sweating in the sciatic distribution.

After removal of the 3rd left lumbar ganglion and part of the sympathetic chain, the relief was immense; the burning and aching went; the pins and needles remained, but the feeling had lost its painful quality; it remained a kind of tingling, "the kind of feeling one has when one's fingers warm up after playing with snow, a feeling of heat"; there were no more surges of pain.

Case 2.—Pte. B. (Partial sciatic lesion.) A painful feeling of pins and needles in the foot and in the dorsum of the toes became worse, until it varied between a terrible burning pain and a feeling like millions of red-hot needles sticking into it. The patient also had an aching pain in the dorsum of the foot, but "this is bearable." The pins and needles were never absent; they were aggravated by noises, and also by draughts, and by cold water. The pain had originated six hours after wounding.

There was almost complete absence of sweating in the peroneal distribution; there was a little sweating between the first two digits; sweating was normal in the tibial distribution. It was found that cold water increased the pain.

Case 3.—Pte. N. (Partial sciatic lesion.) A throbbing pain in the toes and the dorsum of the foot became during five days a terrible burning pain felt superficially. This occurred in bursts, which were superimposed on a lesser continuous pain. The pain was absent on waking, but started as soon as he swung his leg over the side of the bed. It was relieved by keeping the leg beneath cold water. The pain had originated fifteen minutes after wounding.

There was no sensory loss, and sweating was normal.

Case 4.—Pte. M. (Partial sciatic lesion.) This patient complained of a continuous, very severe, gnawing, toothache-like pain all through the sole and heel; it was most severe along the outer side of the foot. Sometimes it was like fire; when it was at its worst, it was accompanied by pins and needles in the toes. It was aggravated by excitement, physiotherapy, or by anyone coming to examine the limb; also by noise, a chair squeaking along the ground, or by an aeroplane passing. "A sudden noise will go straight through my body to my foot." It was seen that when any of these stimuli occurred, he became covered in sweat, the leg involuntarily kicked, and he got a tremor of the other lower limb. The pain was relieved by cold and by absolute rest. The pain had originated eight hours after wounding.

Sensibility was found to be in the state of hypoæsthesia with raised threshold to painful stimuli and increased sensitivity when this threshold was passed. He had hyperhydrosis along both sides of the foot. The kicks of the limb which he described were frequently seen, and were accompanied by exacerbations of pain.

The sciatic nerve was injected above the lesion with 0·25 per cent. Planocaine; this caused a sudden shoot of severe pain in the toes, followed by hypoæsthesia and almost complete analgesia in the sciatic distribution; there was no sweating except in the distribution of the long saphenous nerve. Complete relief of the causalgia resulted; he also had no shooting pins and needles pain; he was able to move the limb with impunity; all that remained was a slight ache in the heel. An attempt was made to bring on the pain by hanging the limb down; very quickly the skin became red; after two minutes he got a dull ache in the foot. The effects of this local anæsthetic lasted twenty-four hours; he considered that the pain remained less following the injection.

Case 5.—Pte. Co. (Partial lesions of median and ulnar.) The fingers felt sore. and were the seat of a constricting, burning pain. It felt as though they were held tightly together, solid, in an extended position; at times it felt as though they were going to burst open. He also had "a burning pain—that is the nearest I can get to a description of it." This came on mainly during the heat of the day; it was also brought on by faradism. It was severe enough to stop him reading or concentrating on anything, and was relieved by holding his hand under the cold tap. At the time of examination it fitted in accurately to the median distribution, but had previously been more extensive; it felt as though it was in the skin or just deep to it. Later the pain lessened, and was described as "a tightening up feeling, as though someone were gripping me between the thumb and first finger and down the middle finger." During the winter, he found that the pain was better when the weather was cold, and he noticed that whenever the fingers were cyanosed he had no pain. The pain had originated one and a half minutes after wounding.

Sensation was found to be in the state of hypoæsthesia with raised threshold to painful stimuli with hypersensitivity when this threshold was passed. There was no sweating in the area supplied by these nerves.

Case 6.—Pte. McL. (Complete sciatic lesion.) He noticed a feeling like a vibration running up and down the outside of his sole every now and then. It became worse during the course of a week, remaining at its maximum for a month. Then it felt like a red hot wire, a vibrating pain, somewhat like pins and needles, but infinitely worse; it was present all the time, but varied in intensity. He discovered no relieving factors; it could be brought on by knocking his leg, and it was always worse at night. It had originated one week after wounding.

It was found on examination that there was complete anæsthesia and no sweating in the sciatic distribution.

Case 7.—Gdn. Bal. (Partial lesions of median and ulnar.) He had a pain in the palm and fingers, which felt as though it were tearing the flesh all the time; added on to this, a pain would shoot down his arm with a bursting feeling. He insisted that it was not burning, but was like claws tearing at the flesh; but the shoot of pain did feel red hot, lasting less than a second. He could hardly walk on account of the pain, and for the first few months after wounding he could not sleep; he would willingly have had his arm cut off to be rid of the pain. It was aggravated by hot weather, noise, and aeroplanes passing; such factors intensified the permanent pain and also brought on the shoot of pain. It was so easily set off in this manner that he dared not look at his fellows fighting about in the ward, as this would bring it on. Having the part stroked with cotton-wool caused excruciating pain; when the pain was at its height, passing a hand 2 inches above it would aggravate it. It was relieved by cold water. The pain had originated on the day after wounding.

There was complete anæsthesia over a large ulnar area, and diminished sensation in the median area: there was no sweating in either area.

After a stellate ganglionectomy, all the pain went. The hand remained feeling warm, but not unpleasantly so; some of the aching had also gone.

Case 8.—Dvr. W. (Complete median and partial ulnar lesion.) This patient had a terrific pain in the hand, wrist and fingers; it was a kind of electric pain, like vibrating shocks; in the palm it felt red hot burning. He also had a soreness; "When the pain gets bad, I call it burning." If he rubbed the limb near the elbow-joint, he got a shoot of pain in the fingers, like terrific pins and needles or electric shocks. The pain had originated within the first week after wounding.

There was anæsthesia and anhydrosis in most of the ulnar and median area, but in the proximal inch of this area there was hypoæsthesia and raised threshold to painful stimuli, with increased sensitivity when this threshold was passed.

Case 9.—Pte. Bu. (Complete tibial lesion.) Two months after being wounded this patient developed an intermittent pain in the foot. It was felt throughout the foot, equally in the parts supplied by the involved tibial nerve and the normal peroneal nerve. The pain was sometimes a burning, and sometimes a pins and needles feeling, "like electricity." It was liable to come on after much walking, and was also brought on by rubbing his finger behind the medial part of the medial malleolus. It also came on when the limb warmed up after being cold, but putting the limb in hot water had no effect. When it was severe, it shot two or three times a minute, and was severe enough to prevent him sleeping.

There was no sweating and complete anæsthesia on the sole of the foot.

Case 10.—Sgt. A. (Complete sciatic lesion.) Very soon after he was hit, this patient developed a burning pain across the dorsum of the foot and in the ankle. Within a day or two it reached its maximum, and remained "a terrific pain" for a month; when at its worst, it also spread into the leg. It was a continuous pain, but was relieved a little by having the ankle passively moved. It gradually diminished after the first month.

There was anæsthesia and anhydrosis in the distribution of the sciatic nerve.

The Relation Between the Pain and the Kind of Peripheral Nerve Lesion.

These pains of peripheral nerve lesions can be considered in three groups: causalgia, pins and needles pain, and deep pain. The distribution

of these three types of pain in a series of 160 peripheral nerve lesions will be shown.

Table I shows the nerves involved in 22 cases with causalgia, extracted from these 160 lesions.

TABLE I

Nerve involved	*Number of cases*
Sciatic	7
Median	7
Peroneal	3
Ulnar	3
Tibial	1
Musculo-cutaneous of upper limb	1
Total	22

Table II shows the number of cases of each nerve involved in the 160 lesions, and the distribution of the three kinds of pain in these cases.

TABLE II

Nerve	*Number of cases*	*Number with causalgia*	*Number with pins and needles pain*	*Number with deep pain*
Sciatic	22	7	6	6
Median	34	7	6	5
Peroneal	23	3	5	2
Ulnar	40	3	5	0
Tibial	7	1	1	0
Radial	30	0	0	0
Musculocut.	3	1	0	1
Axillary	1	0	0	1
Total	160	22	23	15

NOTE.—In these tables, "radial" includes lesions of the posterior interosseous nerve only. "Sciatic" includes lesions above and at the bifurcation of the nerve.

It will be seen that a third of sciatic nerve lesions have causalgia, and a fifth of median lesions. Thus this series does not lend support to the usual belief that this pain occurs mostly in median lesions. The evidence of this series in this respect accords with that of others working on peripheral nerves during this war. The origin of the erroneous belief is likely to be that in fact more median nerve lesions are seen than sciatic, the proportion of median to sciatic lesions being 1·6 to 1; this ratio in peacetime is probably even higher in favour of the median. Median and sciatic lesions formed 21 per cent. and 14 per cent. of the total number of peripheral nerve lesions at the Centre, and they each formed 31 per cent. of the number of cases with causalgia.

It will be seen from the table that ulnar and peroneal lesions are more likely to show pains of pins and needles type than causalgia.

In this series, no radial lesion was found manifesting pain. But causalgia has been recorded with such lesions by Mann (1915), Kinnier Wilson (1927), Pollock and Davis (1933), and Spiegel and Milowsky (1945). The first case ever published, that of Denmark (1812), was that of a patient who had a missile embedded in his radial nerve.

Of the 22 patients who had causalgia, 18 had partial lesions, and 4 had complete lesions. Many workers believe that causalgia occurs only in partial and never in complete lesions; indeed, it is even held that the presence of spontaneous pain shows that the lesion is incomplete. The descriptions of the pains of three cases with complete lesions, and one in which the lesion was probably complete, has already been given (Cases 6, 8, 9, and 10). Further evidence of the type of lesion is given below.

Case 6 (Pte. McL.).—At operation (performed by Col. H. A. Brittain, R.A.M.C.) the sciatic nerve was found to be completely divided; on the proximal end was a large hard neuroma.

Case 9 (Pte. Bu.).—At operation the tibial nerve was found to be completely divided, there being a gap of 3 in. to 4 in. between the two ends.

Case 10 (Sgt. A.).—Operation was persistently refused. Over a period of 240 days, there was no motor, sensory or sudomotor recovery, no triple response, and no positive Tinel's sign.

Case 8 (Dvr. W.).—Over a period of 128 days there was no sign of regeneration in the median, but this period was too short to be sure that no regeneration was occurring.

The popular view, that causalgia occurs only in partial lesions, is doubtless due to the clinical impression caused by the actual preponderance of partial over complete lesions exhibiting causalgia. In these 22 cases with causalgia, only 4 had complete lesions; the ratio of partial to complete is therefore 5·5 to 1. In war casualties, partial lesions of peripheral nerves are twice as common as complete ones; the numbers found in 134 cases were 92 partial lesions, 42 complete.

The Site of Origin of the Pain Impulses.

It will now be shown that in all peripheral nerve injuries with causalgia the pain impulses arise in the central end of the damaged nerve, and not in the peripheral end of the nerve, and not in the region which is felt to be painful.

Lewis (1936) suggested that causalgia was to be explained as follows: "The suggestion is that chronic irritation of a peripheral nerve stimulates nerve-fibres of the posterior root system to distal action, thereby releasing

substances in the skin which induce a state of local erythalgia, with or without herpes, and that it is from the skin so affected rather than from the nerve at the seat of injury that much or all of the pain arises, the pain impulses being conveyed back along the same nerve, or along a nerve supplying overlapping branches to the common territory." He is supported in this view by Gask and Ross (1937), who state that causalgia and an accompanying "vasodilatation of the minute vessels, wasting, glossy skin and herpetic eruptions are all to be explained by the release of 'H'-substance by antidromic impulse. Sympathectomy leads to the washing away of this 'H'-substance, and this abolishes the peripheral manifestations of causalgia."

If this suggestion accords with the facts, then the following two conditions will be found:

(1) There will be an intact pathway of some sort from the skin in which the causalgia arises.

(2) The skin will be in a state of erythralgia.

(1) Causalgia occurs in cases of amputation. Livingston (1943) has stated that it is the commonest pain of such cases. Descriptions of their pains have been obtained from 10 patients with amputation of limbs or digits which were painful; these descriptions will not be given here; suffice it to say that these pains included causalgia. In these cases the pain impulses must arise in the nerve trunk, and they arise presumably at the site of the lesion on the nerve.

In peripheral nerve lesions other than amputations, it is conceivable that the pain impulses could arise in the region below the site of the lesion on the nerve trunk. The pathways they could use to the C.N.S. are (*a*) the somatic sensory nerves from the area; (*b*) the somatic proprioceptive nerves from the area; (*c*) the sympathetic nerves from the area.

An examination of the nervous pathways below the lesion was undertaken in 12 cases with partial lesions; these cases include those the description of whose pain has been given.

(*a*) *Somatic sensory innervation.*—The absence of somatic sensory innervation was shown in 6 cases by sensory examination and by the triple response, as suggested by Lewis (1936). These cases showed complete anæsthesia, and no flare on pricking the skin through histamine. Partial somatic sensory innervation was present in 6 cases. This was shown by the presence of diminished sensation or by hypoæsthesia with raised threshold to pinprick. (One case came into both groups, as it was first examined when in the first, later when in the second group.) The presence of somatic sensory innervation was shown by one case, which had no sensory disturbance and

an equal flare on the two limbs. It follows that causalgia may be referred to an area, whether that area has somatic sensory innervation or not.

(*b*) *Somatic proprioceptive innervation.*—4 cases had no innervation of the muscles underlying the painful area. 9 had innervation in some of the muscles. It follows that causalgia may be present in an area, whether the muscles of the region have an intact nerve supply, or not.

If the pain impulses of causalgia were arising in the area which is completely denervated, it could still be argued that they travelled via the adjacent nerves overlapping the denervated area. This, however, entails the conception that the pain due, say, to a median nerve lesion, and well localized to the median area, is travelling up the ulnar and/or radial nerves, and yet interpreted as coming from the median area. Such a conception is absurd. If it be considered possible that impulses could travel in overlapping nerves, it would be assumed that in cases of causalgia associated with combined lesions of median and ulnar—a common combination—the pain impulses would travel in the superficial radial nerve, even though the pain is not felt in that distribution. There were 2 cases in this series with complete lesions of the sciatic nerve; if the pain impulses were considered to be arising in the denervated area, they would have had to reach the C.N.S. by the saphenous nerve, a nerve supplying an area at least 6 cm. from that in which the pain was felt.

Nevertheless, the hypothesis of conduction by overlapping nerves was tested in one case. It follows.

Case 11 (Pte. Ch.).—This patient had complete anæsthesia and complete anhydrosis in the distribution of the median, radial, and lateral and dorsal cutaneous nerves of the forearm. The only remaining pathway from the hand and fingers, from which his severe pain could be thought to come, was the ulnar nerve. The ulnar was blocked by an injection of 2 per cent. novocain; this gave an immediate rise in temperature of the ulnar fingers of 6° C., and complete sensory loss. But there was no alteration in the pain.

(*c*) *Sympathetic innervation.*—A sweating test was performed. After having a pint of hot tea the subjects were laid out in the afternoon sun during the summer in Palestine. The limb to be tested was sprinkled with "Quinizarin" (kindly given by Messrs. Burroughs Wellcome). Sympathetic denervation of the skin was proved in 10 cases. The presence of sympathetic innervation was shown in 3 cases; 1 showed sweating, but it was less than normal; 2 showed profuse sweating. It follows that causalgia may be present in an area, whether that area has a sympathetic innervation, or not.

It will be seen that (with one exception) all pathways from the area from which the pain might originate have been shown to be incapable of

conducting in some cases of causalgia; if the exception is left aside, it can be concluded that the pain is therefore not arising in the tissues deprived of their normal nerve supply.

The exception is a possible pathway that has not yet been considered: the nervi vasorum and sympathetic network surrounding the vessels of the otherwise denervated part.

It is usually held that the great vessels of the limbs receive their sympathetic innervation from the brachial and lumbosacral plexuses; this source is thought to supply the vessels only for a few inches; further distally the vessels are thought to rely on the peripheral nerves of the limb for their sympathetic supply. If this is so, it will be seen that in those cases where the absence of a sympathetic supply was proved by a sweat test, the vessels must also have been denervated.

It is possible, however, that an afferent pathway may be formed by the continuous chain of sympathetic fibres surrounding the main vessels of the limbs. This plexus might drain into the C.N.S. by two paths: it might use the path of the peripheral nerves, where these connect to it in the nervi vasorum; and/or it might pass from the subclavian arteries or the aorta into the sympathetic chain, and thence into the C.N.S. via the white rami and the posterior nerve-roots.

That pain impulses can travel along this plexus in this manner is denied by Carmichael and Stürup (1935). They blocked the ulnar nerve at the elbow with 4 per cent. novocain, causing loss of position sense in the 5th digit. They then laid bare the artery at the base of the 5th digit, stimulated it faradically, pulled it, stretched it, and clamped it; no pain was felt.

This possible pathway has been investigated in animals. Friedreich (1924) concluded that pain from the great vessels travelled by the periarterial nerve plexus; but more recent work by Gilding (1932) and Moore and Singleton (1933) has brought evidence entirely in the opposite direction.

On the clinical side, Foerster (1927) has presented evidence that pain can be conducted via afferent sympathetic nerves, running in the network surrounding the arteries of the limbs. He states that a limb which has lost its afferent and efferent spinal innervation can still transmit pain on strong pressure, of a dull, diffuse type. He observed one case of a rupture of the brachial plexus from C4 downwards, distal to the joining of the sympathetic nerves; the intercosto-brachial nerve was also torn; these clinical findings were confirmed at operation. This patient felt dull pain on hard pressure on his fingers. Foerster states that the only possible pathway was the periarterial plexus of the branches of the subclavian artery, ending finally in the thoracic chain, thence into the posterior horn. He recorded another

case of a patient, who, after section of the posterior roots of C7 and 8, and Th1 felt definite pain on firm pressure applied to the otherwise anæsthetic little finger; at operation no pain was experienced on electrical stimulation of the nervus proprius volaris of the little finger, but pain was felt on stimulating the artery of the little finger. Foerster, Altenburger, and Kroll (1929) have reported the case of a man with a complete lesion of the tibial nerve, confirmed at operation. He could feel pain when the sharp end of a pencil was pressed into the sole of his foot. When the popliteal artery was stripped, he experienced severe pains in the sole of his foot; after this operation, no form of stimulation could induce any sensation in the sole. Leriche (1937) also reported a case of a patient who after tearing of the brachial plexus showed anæsthesia and analgesia, and yet he had pain when his brachial artery was pinched.

In spite of this evidence that there may be an afferent pathway from an otherwise deafferented area in the shape of the sympathetic chain surrounding the vessels, it is obvious that this is not the pathway for conduction of the impulses of causalgia or pins and needles pain. The pain of arterial puncture has been carefully described by Bazett and McGlone (1928) as dull, aching, diffuse, usually distally referred: this is not causalgia.

We may conclude that the only pathway found in all cases of lesions of peripheral nerves with causalgia, whether complete or partial, is the nerve above the lesion; all others, when they exist, have been shown to be absent in the presence of causalgia. Therefore the pain causalgia must arise at the site of the lesion on the wounded nerve.

(2) The characteristics of the state of erythralgia are (*a*) that there is a response to needle-pricks which are too light to arouse pain in normal skin, and that this response, when aroused, is of unusual intensity and more diffuse than normal; (*b*) that the same response can be aroused by friction which would not normally arouse a painful response; (*c*) that the same response can be evoked by warming and cooling the skin at temperatures which do not evoke pain in normal skin; (*d*) that this painful response is increased by raising the tension in the veins and venules, and relieved by decreasing it again.

The 16 cases of this series were investigated to find out if the state of erythralgia was present or not.

(*a*) Lewis (1942) emphasized that the skin in the erythralgic state "is truly hyperalgesic, in the sense that it responds to needle-pricks that are too light to awaken pain in surrounding unaffected skin," and that this response is unusually intense and diffuse. In 10 of these 16 cases there was complete analgesia and anæsthesia; they therefore had no hyperalgesia. In the other

6 cases, there was hypoæsthesia, and a raising of threshold to pin-prick and hair-pulling; but when this threshold was passed, the pain was more intense and diffuse than the pain felt with the same strength of stimulus on normally innervated areas.

(*b*) In these 6 cases there was a degree of hypersensitivity to friction quite different from that found in erythralgia. They all avoided the contact of clothes and sheets; blankets were never tolerated, as they caused pain. In two of them, the lightest touch with cotton-wool was excruciatingly painful.

(*c*) The pain threshold to heat and cold is reduced in erythralgia. In the normal human, according to Rein (1925), pain starts to appear when a temperature of 40° is applied to the skin; Lewis (1942) agrees with this figure. Lewis (1924) gave 45° to 47° as the temperature at which pain becomes intolerable, when thick-skinned parts are immersed in hot water; and Lewis and Love (1926) found that heat applied by a metal bar caused intolerable pain at 47° to 47·5° on Love, and at 45° to 47° on Lewis. In erythralgia, pain may come on between 24° and 32°, and commonly comes on at 40°, according to Lewis and Hess (1933).

This sensitivity to temperature was reinvestigated in normal subjects. These experiments were carried out on British soldiers who had been living in the open air for two years in the Middle East. It proved impossible for them to say when pain started, so the temperature investigated was that at which they experienced pain to the extent that they had to withdraw the limb, or that at which it required an effort to keep it there. The limb under test was immersed in a bucket 2 ft. deep; the bucket was filled with water at the required temperature. The temperature of the water was taken by a mercury thermometer measuring 1 cm. per degree, which was attached to a mixer, so that the temperature of the water could be made the same throughout. The temperature was raised 1/10th of a degree at a time; when it was adjusted the man had to put the limb in the bucket.

The following figures were obtained: Hands and forearms: 22 subjects; Range 44·4° to 48°; Av. 47·1°. Feet and legs: 19 subjects; Range 44·2° to 48°; Av. 46·2°. It is seen that the range for all four limbs is the same, and that the mean threshold figure is 46·7° ($\sigma = 1{\cdot}7$). It was considered that 1° was within experimental error.

The figure obtained thus agrees with that of Lewis.

The following cases were also investigated in the same manner; 8 cases of peripheral nerve lesions with causalgia; Range 44·4° to 47·9°; Av. 46°. 11 cases of peripheral nerve lesions without pain; Range 45·2° to 49·2°; Av. 47·4°. 1 case of previous causalgia with partial peripheral nerve lesion

and stellate ganglionectomy: 44·5°. 1 case of partial peripheral nerve lesion without causalgia with lumbar sympathectomy: 45·2°.

In the cases with causalgia, there was no significant difference between the affected limb and the normal one. σ being 1·7°, it is seen that no figure is twice this; therefore no figure is significant; indicating that cases with peripheral nerve lesions, with or without causalgia, with or without sympathectomy, have the same pain threshold when tested by raising the temperature of surrounding water, as normal controls. Thus, unlike the state of erythralgia, in causalgia there is no hyperalgesia to temperatures which are painless in normal humans.

(*d*) The effect of changing the venous tension in the area was investigated in 14 cases with causalgia.

Of the 14, 6 found their pain aggravated by hanging down the limb, then relieved by elevating it. In one other case, the manœuvre had no effect on the causalgia, although dependence brought on pins and needles, which was relieved by elevation. 2 patients stated that any change in position eased the causalgia. One found that hanging the limb down or elevating it brought on the causalgia. 4 patients found that the position of the limb had no effect on the pain.

The effect of blocking the venous return was investigated. The observation of Lewis and Hess (1933), that the pain due to changes in the pressure of veins and venules is independent of skin temperature change, was confirmed; for in no case was the change in position of the limb accompanied by a change in temperature of more than 2°.

In Case 5 (Pte. Co.), with a sphygmomanometer pressure of 45 mm. of mercury for nine minutes, the pain which was present on starting went away.

In Case 12 (Tpr. H.), with a sphygmomanometer pressure of 45 mm. of mercury for ten minutes, there was no pain.

In Case 6 (Pte. McL.), with a pressure of 45 mm. for five minutes, there was no pain.

In Case 13 (L/Cpl. K.), with a pressure of 45 mm. for ten minutes, there was no pain.

In Case 11 (Pte. Ch.), with a pressure of 40 mm., the pain became so severe that he could stand it for only one and a half minutes; on release of the cuff, the pain went.

In Case 3 (Pte. N.), with a pressure of 40 mm., he could stand the pain only one minute. In addition to bringing on the causalgia, it gave him the feeling that his big toe was in a vice. Both pains went twenty seconds after release of the cuff.

In Case 2 (Pte. B.), with a pressure of 40 mm., the causalgia came on after ten seconds. It went within ten seconds of the release of the cuff.

It is seen that there is no one constant effect on the pain of increasing the venous pressure; in this, the pain of causalgia differs from that of the erythralgic state.

It has thus been shown that in causalgia associated with peripheral nerve lesions, the skin is not in a state of erythralgia. In erythralgia there is true hyperalgesia, there is a lowering of threshold to the pain caused by heat and cold, and the pain is always increased by raising the venous pressure; these factors are not found in causalgia; also the response to friction is different in the two conditions.

The two conditions necessary to Lewis's hypothesis have been shown to be absent in cases of peripheral nerve lesions with causalgia. As there is no constant pathway from the region in which the pain is felt to be, and as this pain is felt to be in areas which are completely denervated, and as it is felt to be in the same area when this area is a phantom, in cases of amputation, it is concluded that the pain impulses arise at the site of the lesion on the central end of the nerve, and that the pain is referred by the subject to that region which is normally drained by the nerve involved.

The Role of the Sympathetic System in Pain Conduction.

Our knowledge of the role of the sympathetic system in the conduction of sensation is incomplete and much of it is conflicting. It will now be considered.

The effects of stimulating the sympathetic, in animals.—Davis and Pollock (1932) stimulated the superior cervical ganglion in lightly anæsthetized cats; the animals gave evidence of having pain. By cutting the various branches of the ganglion, they showed that the pain pathway was the branch to the carotid plexus; from here, it was either the posterior spinal roots or the anterior or posterior root of N5. The anatomical details, however, need not concern us here. It is sufficient to point out that stimulation of a sympathetic ganglion can cause pain.

The effects of sympathectomy on sensation, in animals.—The first observation on changes in sensation effected by sympathectomy was made by Claude Bernard (1851). He found that after removing the superior cervical ganglion from one side of a cat or a rabbit, sensation in the corresponding part of the face was *increased.* He pointed out that as this increased sensitivity was difficult to demonstrate "par les moyens ordinaires," it was necessary to decrease the general sensitivity of the animal in some way, so that the increased local sensitivity would stand out. To do this he used a dilute solution of curare; then he found that "toutes les parties du corps où le sympathique n'a pas été coupé deviennent insensibles avant le côté de la face où le ganglion cervical a été enlevé."

No notice of these observations was taken for eighty years; then Tournay (1932) made similar experiments with the same results. The same

phenomenon was discovered independently by Dusser de Barenne (1931).

It is seen, then, that sympathectomy resulted in increased sensitivity in experiments on animals.

The effects of sympathectomy on sensation, in man.—This phenomenon having been observed by three distinguished physiologists, it is surprising to find that clinicians are almost unanimous in declaring that sympathectomy has no effects on the sensation of the affected part. It is true that Pette (1927) has reported in 4 cases the development "sehr bald nach der Operation" of tenderness in the bones and on pressure of the denervated parts; but he did not consider the possibility of injuring the somatic nerves of the cerebrospinal system during the operation; nevertheless the fact that 2 of his patients who had had a cervical sympathectomy developed a pain in the eyeball of the affected side shows that this pain at any rate could not have been due to injury to spinal nerves. Brown and Adson (1929) noted cutaneous hyperæsthesia in some degree in every case after thoracic ganglionectomy; it was associated with soreness of the muscles, nerve-trunks and large arteries of the arm; it diminished in ten to fourteen days, and was gone in four to five weeks; they suggested that it was due to damage to Th1 and 2 spinal nerves, and pointed out that it was minimal when damage to these nerves was most carefully avoided at operation.

On the other side, we have the opinions of all other surgeons who have performed these operations, that no changes in sensation are ever observed; using the routine clinical tests of sensation, I have never found any changes in sensation in limbs which have been sympathectomized.

The sensation in regions having only sympathetic innervation.—Owing to the manner in which the sympathetic outflow is distributed to the lower limbs, it is common to find in lesions of the lower spinal cord or cauda equina areas of skin which are deprived of an intact somatic nervous pathway yet which have a normal sympathetic innervation. As the sympathetic from these areas reaches the C.N.S. above the level of the lesion of the cord, impulses subserving sensation from these areas could reach the cortex, provided the sympathetic system could be used as an afferent pathway.

Two cases of cauda equina lesions were investigated from this point of view.

Case 14 (Rfn. Bud.).—This man was wounded by a bullet passing through his back from one side to the other; it removed the laminæ of L2; at operation the division of the cauda equina was found to be complete.

When investigated one week after wounding, it was found that the patient had no voluntary movement of either lower limb, and complete areflexia below the lesion; there was no form of sensibility below Th12 on the left, and L1 on the right.

A sweat test was performed. His lower limbs were exposed and their dorsal surfaces sprinkled with quinizarin. Sweating was induced by giving hot tea by mouth, and by heating the upper trunk and upper limbs under a radiant heat cradle. From fig. 1 it will be seen that there is a large area in which sympathetic innervation is present, but in which there is no form of sensation.

Case 15 (Cpl. D.).—This man was wounded by a piece of mortar shell which lodged in his spinal canal at the level of L1. He had complete loss of reflexes, tone, and movements below this level, and no form of sensation.

A sweat test was performed as above. From fig. 2 it will be seen that there is a large area in which there is sympathetic innervation, but no form of sensation.

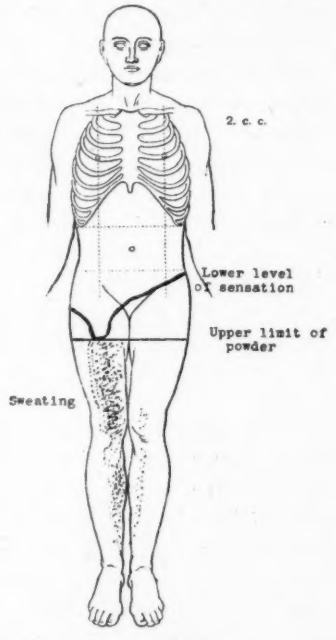

Fig I (Rfn Bud)

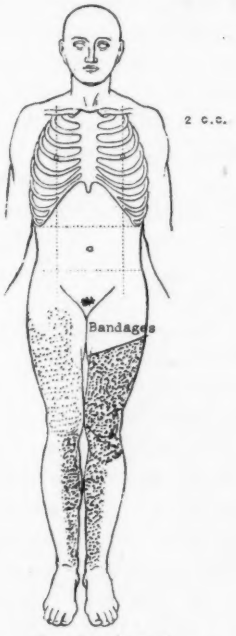

Fig. 2. (Cpl D)

Thus it is seen that in these two cases no form of sensation was conducted via the sympathetic system.

Some evidence for sympathetic conduction of sensation has been recorded by Helson (1932). He found that in some patients who had previously had the trigeminal sensory root successfully sectioned, and who had had a return of some burning pain, that cylinders at 50° to 75° C. held against the facial skin caused stinging and pricking. After a "thoracic sympathectomy" had been performed on three of them, their skin could even be seared without any sensation except that of pressure.

Similar evidence for deep pain conduction has already been quoted from Foerster (1927), Foerster, Altenburger, and Kroll (1929), and Leriche (1937). One further case of Foerster's is relevant here, in which conduction must have been either via the nervi vasorum and plexus running up the tibial, popliteal, femoral, iliac arteries, thence from the aorta into the sympathetic chain, or via the sympathetic accompanying the peripheral nerves, thence via the rami communicantes from the lumbosacral nerves to the sympathetic chain. It is the case of a gunshot wound of the cauda equina, which caused severe pain; in order to relieve the pain, root section Th12 to S5 was performed. This not only did not cure the pain, but pressure sense remained in the leg, and a diffuse pain could be produced. Foerster, Altenburger, and Kroll reported two further cases of pain conduction from the soma along the sympathetic chain. One was a case of traumatic paraplegia at Th6, which was seen at operation to have a gap of 2 cm. between the two portions of the divided cord; this patient sustained a fracture of the thigh; when the fragments of the bones rubbed against each other, she complained of severe pain. In the other case there was complete division of the cord at Th8, so that at operation the lower portion could be lifted out of the dural sac; this patient complained of "hellish pains" when forcible straightening of his legs was performed. In these two cases the only pathway from the limbs to the C.N.S. was along the lumbar sympathetic chain.

The sensation on stimulation of the sympathetic, in man.—The next experiment to do in man is to stimulate sympathetic nerves and find out if pain or any form of sensation results. This has been done by Foerster, Altenburger and Kroll (1929), and by Shaw (1933). Foerster *et al.* found that manipulating the cervical sympathetic trunk caused pain; they then cut the trunk and stimulated the central end, again producing pain. It is unfortunate that they did not go on to stimulate the peripheral end—an experiment which has not been performed in man. They found that touching the stellate ganglion caused pain in the upper limb; and, similarly, that irritating the lumbar chain caused pain in the leg, and that electrical stimulation of the central end of a sectioned ramus communicans of L4 caused severe pain in the inner side of the leg, extending down to the internal malleolus. Shaw also performed a cervicothoracic ganglionectomy under local anæsthesia. He pinched the upper pole of the ganglion, producing a sensation of touch which the patient referred to the region of the axilla. He then crushed the ganglion with artery forceps; this "caused excruciating pain of a burning and gripping character, which was felt inwardly over the region of the heart. This pain did not follow instantly after the

crushing, but began after a latent period of a few seconds, increased in intensity for an appreciable time, and after some minutes, gradually waned and died away. On removal of the ganglion by traction on the thoracic chain, a similar outburst of pain was excited, which lasted about twenty-four hours."

The time-lag between stimulation and the sensation of pain is an important phenomenon, marking off stimulation of the sympathetic from stimulation of a cerebrospinal somatic nerve, where the pain is always felt immediately; this difference indicates that the mechanism of conduction of sensation is unlikely to be the same in the two systems. As it is possible that the sympathetic influences sensation and its conduction by having efferent functions, it is important to stimulate the peripheral end of a cut sympathetic nerve in man. The above experiments leave no doubt that stimulation of the sympathetic in man causes pain. It will be noted that this is not what one might have expected, knowing that extirpation of the sympathetic in animals caused hyperæsthesia and hyperalgesia.

Fortunately the surgeons have not been daunted by this as yet incomprehensible and incompatible evidence culled from experiments, but have gone ahead with sympathectomies in various painful states, collecting ample evidence that the operation stops the pain in some of these conditions. This will now be summarized.

(*a*) *Sympathectomy for causalgia in peripheral nerve lesions.*—Evidence concerning the therapeutic value of sympathectomy in causalgia will not be given here, as it is well known; indeed ganglionectomy is now the routine surgical procedure for causalgia with lesions of peripheral nerves. The results of this operation in these cases have been reported by Spurling (1930) and Speigel and Milowsky (1945) in America, Kwan (1935) and Wan (1943) in China, and by Ross (1935) in this country. It is to be noted that sympathectomy cures the burning pain only; in the two cases in the series presented here, sympathectomy did not stop the pins and needles sensation or the aching.

(*b*) *Sympathectomy for pain of phantom limbs and amputation stumps.*—It is known that the pain of amputation stumps and of phantom limbs can be stopped by surgical or chemical blocking of the sympathetic nerves concerned.

Friedreich (1924) reported the case of a man who had had a finger amputated. Six months later, the man got a terrible pain in the adjacent finger; this was consequently amputated. He remained free from pain for two months, when the pain came into the whole hand; for this, the

hand was amputated. In three months' time he got the same pain in the amputation stump; for this the neuroma was removed, with no benefit; the three peripheral nerves of the limb were then cut, also without benefit; the effect of anæsthetizing the brachial plexus was tried, but it failed to alter the pains. A sympathectomy was then performed; within three days the pains had gone.

White (1930) quotes the case which he saw at Professor Leriche's clinic in Strasbourg, of a man who had had five successive amputations, starting with a crushed finger, and ending with a frightfully painful stump of his upper arm. After a posterior root section had failed to help him, he was cured by the removal of the stellate ganglion. He reported a further case of his own, of a man who had had his crushed finger-tip amputated. This was followed by severe aching along the inner aspect of his forearm, radiating at its maximum into his right chest; blocking the nerves at the base of the finger with novocain had no effect. After an experimental novocain paravertebral injection of Th1 and 2, a removal of these ganglia was carried out; this completely relieved the pain.

Stammers (1932) reported the case of severe pain and tenderness in the stump of an amputated thumb, which was cured by cervico-thoracic sympathetic ganglionectomy; a second case relapsed after three weeks, but he considered that the operation had been incomplete, as no Horner's syndrome had been obtained.

Leriche (1937) reported a case of a man with an amputation through the thigh, who for years had crises of pain in the stump and phantom foot; he was cured by injection of the lumbar sympathetic with novocain. He has repeated this experience in other cases, and Leriche and Fontaine (1934) recommend this anæsthetizing of the sympathetic as the routine treatment of painful stumps or phantoms.

Livingston (1938) reported 8 cases of phantom limb pain, consisting of cramps, terrible feelings of tension, boring pains, feelings of constriction, aching, feelings that the skin was being stretched, as though the flesh were being torn, burning heat, and shooting pains, which were relieved by injecting the stellate ganglion with novocain, and/or the first seven dorsal sympathetic ganglia. His patients then felt that they could move their fingers one by one, their phantoms felt relaxed and pleasantly warm, and the feeling of tension had gone. Objectively, the involuntary jerking of the muscles above the stump ceased, and the stumps and the neuromata were no longer sensitive to firm handling.

Doupe, Cullen and Chance (1944) record a case which showed com-

plete, but only temporary, relief of "tight and searing pains" in phantom digits and hand, after novocain block of the stellate ganglion.

Walker (1942) recorded a case in which the pain in a phantom hand was aggravated by novocain block of the cervical sympathetic chain.

(*c*) *Sympathectomy for post-herpetic neuralgia.*—Hyndman (1939) has reported the case of a man who had herpes in front of the left ear, on the left side of the occiput, the left side of the neck, the left upper limb, and on the anterior aspect of the chest in the distribution of the left Th1 and 2; he also developed some deafness on the left, and dizziness. The herpes left "a spreading, unpleasant pain when any of these zones were brushed with the fingers." There was also severe pain felt in the left tympanum when the patient swallowed. The patient underwent two operations. In the first, the left splanchnic nerves were removed with the 1st and 2nd dorsal lumbar ganglia; this resulted in the cure of all the hyperæsthesia below the left clavicle, including that of the left upper limb. In the second, the stellate and the upper three thoracic ganglia on the left were removed; this stopped all the rest of the pain and hyperæsthesia, and swallowing was no longer painful; the ear and great vessels were no longer tender. This cure had remained for five months at the time of reporting.

Leger and Audoly (1942) reported two cases of herpes zoster in which the pain was relieved by infiltration of the homolateral stellate ganglion. It is to be noted that this caused no effect on the course of the eruption; it only removed the pain.

Leriche (1937) and Dechaume (1937) state that pains strictly localized to the territory of a spinal nerve can be stopped "de façon durable" (Leriche) by injection of the appropriate sympathetic ganglion with novocain. Dechaume states that this occurs even in the presence of an obvious lesion of the cerebrospinal nerve, and lasts a few hours; it is accompanied by no objective changes in sensation, for, on testing, the patient still feels deep and light touch, and warm and cold: "les récepteurs sensitifs, les voies cérébro-spinales n'ont pas été modifiées et cependant le patient ne souffre plus." The three cases of herpetic neuralgia cured by functional sympathectomy are evidence of the correctness of this statement.

(*d*) *Sympathectomy for other painful states in the soma.*—Shaw (1933) has reported cases of severe aching and burning pain in the limbs, of unknown pathogenesis or due to a perforating ulcer on the toe, in which the pain was immediately cured by sympathectomy.

In considering all this evidence, we can conclude (*a*) that sympathectomy increases the sensitivity of the affected region in rabbits and dogs; (*b*) that sympathectomy has no similar effect in man; (*c*) that the evidence

of sympathetic afferent function in the soma in man is inconclusive; (*d*) that there is a form of pain arising at the site of a nerve lesion which continues only as long as there is an intact sympathetic system accompanying that nerve or supplying its area of distribution.

Hypotheses of the Genesis of Causalgia.

(1) *Vascular stasis.*—A hypothesis to explain causalgia must explain its occurrence in complete nerve lesions, where the skin is totally denervated, as well as in partial nerve lesions, and it must explain its immediate cure by sympathectomy in nearly all cases.

As the abnormal vascular state associated with causalgia in peripheral nerve lesions has been so striking to most observers that they have tried to attribute the pain in some way to this condition, it must be pointed out that all these vascular phenomena can occur in peripheral nerve lesions without causalgia or any kind of pain.

Lewis and Pickering (1935) have shown that immobility alone will lower the temperature of the part; this will cause "increased vascular coloration of the skin," and a loss of the normal furrowing of the skin, giving it a smoother surface. Prolonged disuse will cause atrophy of the fingers.

A diminished blood supply to the part is the result of complete section of a nerve. The inadequate blood supply causes a diminution in temperature of the part, atrophy of the skin and nails and soft tissues and decalcification of the bones; also "in maladies where the reduction in blood flow is considerable and persistent, as in severe Raynaud's disease . . . the fingers may be distinctly swollen." The defective blood supply also results in a "cyanotic tint of the cold fingers or hands; it is due to the slow flow of blood through the skin, which does not differ greatly, if at all, in tint from that of normal fingers at corresponding temperatures." This prolonged cold damages small vessels so that they remain permanently dilated. Further, it has been shown by Grant and Holling (1938) that when an area of skin has been deprived of its innervation, that area will not join in the general vasodilatation caused in innervated skin on heating the body.

Seeing that in cases of peripheral nerve lesions there is both prolonged disuse of the part and a diminished blood supply, the explanation of those phenomena called trophic is clear. This vascular state is not confined to those cases having causalgia; indeed, Hurst (1944) has presented photographs of digits showing œdema or atrophy; these occurred in hysterical paralyses, and were cured by psychotherapy.

As it has been shown that causalgia does not arise in the denervated

or partially innervated region below the lesion, it will be understood that the vascular state of the periphery is irrelevant. It might be supposed that stasis and a poor blood supply of the nerve stump is a cause of causalgia; but we must remember how warming the limb directly or by warming the body, or hyperæmia of the limb caused passively or reactively, does not alleviate the pain, but usually aggravates it.

(2) *Vasoconstriction.*—The main theories of the pathogenesis of causalgia fall into two mutually exclusive groups: those in which it is attributed to vasodilatation; and those in which it is attributed to vasoconstriction. The facts are that vasoconstriction and vasodilatation of arterioles and capillaries do both occur with causalgia; they may neither accompany it; and they can both occur without causalgia, as is well known. They therefore do not stand in direct causal relationship to it (a cause being an invariable precedent of the caused phenomenon).

Leriche is the main protagonist of the view that vasoconstriction causes causalgia. Leriche believes that the irritation of scar tissue acts as a continuous stimulus to a vasomotor reflex. This reflex causes vasoconstriction or vasodilatation in the surrounding parts, vasoconstriction being the commoner result; included in the surrounding parts is the nerve-trunk itself; this abnormal vascular state of the nerve is thought to cause burning pain *per se*. He sums this up by stating that a pain resulting from vasoconstriction keeps the vasoconstriction going, which in turn keeps the pain going. This vasoconstriction causes "une véritable maladie nouvelle." It is unclear what relation there is between this "maladie nouvelle" and the pain of peripheral nerve lesions; although he takes into account that vasoconstrictive spasm is not painful in itself, he states that this new malady is shown by cyanosis, lowered temperature, œdema, trophic disturbances and pains. Why in some cases the same stimulus should cause vasoconstriction and in others vasodilatation, he admits that he is unable to explain. Sympathectomy is thought to cure the pain by breaking the reflex arc, thus restoring a normal vascular state to the part, including the nerve. It will be noticed, however, that the pain is thought to arise from irritation of the axons by scar tissue in the neuroma; sympathectomy will have done nothing to change this. Furthermore, if sympathectomy acts only by causing vasodilatation, why does vasodilatation induced in other ways not cure the condition? One of the nine cases of Speigel and Milowsky (1945) is relevant here; immediately after the pre-ganglionic sympathectomy "there was complete relief of spontaneous pain and complete relief from pain on manipulation of the hand" but for one hour after operation the hand was actually cooler than the control, there being

two days before it became warmer. Leriche in most cases excised the stellate ganglion; following which operation the vasodilatation does not usually last more than months, and the vessels become sensitive to circulating adrenaline. If, then, the pain were due to vasoconstriction, it is reasonable to suppose that it would return when vasoconstriction returns (which does not happen), and the subject would be likely to experience after stellate ganglionectomy very severe pains under circumstances evoking the secretion of adrenaline (whereas such circumstances conspicuously no longer bring on the pain after this operation). In attempting to explain the cure of the pain by invoking the known effects of sympathectomy on the vascular state, it cannot be a matter of indifference whether vasoconstriction or vasodilatation is present. If sympathectomy cures the pain by removing vasoconstriction, it cannot be understood how it also removes excessive vasodilatation in the cases where that is present.

(3) *Vasodilatation.*—Lewis was the main protagonist of the view that vasodilatation causes the burning pain.

Lewis's hypothesis has already been considered. It cannot account for causalgia occurring in complete lesions. In short, he proposes the same pathogeny as is usually accepted for herpes—a different condition. If, as Gask and Ross put forward, sympathectomy cures causalgia by washing away irritative substances liberated antidromically, sympathectomy would not only cure causalgia, but if performed before herpetic vesicles were formed it would prevent their formation. But this does not happen; as is shown by the following important case of Leger and Audoly (1942). A woman aged 45 came to them, complaining of intercostal pain for the previous few days. On examination they found an intercostal oval plaque, reddish, but not vesicular; they made a diagnosis of herpes zoster, still in the pre-vesicular stage. They injected the homolateral stellate ganglion, repeating the injection in forty-eight hours. There was immediate relief of the pain. But the herpes zoster followed its usual course, going on to the usual vesiculation.

That stimulation of nerves coming from the skin causes burning pain is to be expected. Lewis himself wrote (1942): "On experiencing and considering the pain derived from the superficial layers of the skin in response to various stimuli, I am brought more and more firmly to believe that all such pains have but a single quality, and that the variable characteristics of such pains are merely in their intensity and in their distribution in time and space. The quality is the same if the pain is produced by stimulating nerve-endings or nerve-fibres." As all skin pain is burning pain and as stimulating nerves from the skin causes burning pain, it is

unnecessary to suppose that actual damage to the skin has to be done, causing burning pain conducted to the C.N.S. via overlapping fibres, to explain the burning quality of pain in lesions of cutaneous nerves.

Lewis (1942) also states that "if the pain arose directly by irritation of sensory fibres in the main nerve-trunk, it might be anticipated that pain of the deep variety would also be felt from time to time." From the descriptions of the pains of soldiers with peripheral nerve lesions, it is seen that they do complain of deep pain. Such pains are described as gnawing, toothache-like, aching.

(4) *The artificial synapse.*—Foerster (1927) states that the electrical mechanical, or chemical stimulation of the central end of a sectioned peripheral nerve causes terrible pain, provided the stimulus has a certain strength. Sharpey Schaefer (1927) squeezed a sensory nerve on himself with artery forceps, producing "a very unpleasant burning sensation." It is common knowledge that any pain due to irritation in the course of a nerve is interpreted as coming from the area of distribution of that nerve; Dechaume (1937) has put this as follows, with the neatness possible in the French language: "Le malade souffre toujours périphériquement." The simplest explanation of the pain would be: stimulation of the axons is occurring at the point of damage to the nerve; this occurs whether the lesion is complete or partial; the pains are referred to the distribution of the nerve; the pains are those which the nerve is normally able to transmit in response to normal stimuli to the nerve endings. Once this pain is experienced in the limb, the subject will guard and nurse it, avoiding movement—thus increasing the disuse and immobility which are the causes of the vascular disturbance and atrophy.

This hypothesis satisfies the conditions that the pain is explained in partial and complete nerve lesions whether the skin is denervated or not, but it remains unrelated to our knowledge of the role of sympathectomy in this condition.

Doupe, Cullen and Chance (1944) have put forward the hypothesis that the pain is caused by efferent impulses in the sympathetic fibres stimulating the somatic afferent spinal nerves at the point of damage, or possibly at the nerve-endings. This seems to be the most satisfactory hypothesis; for it adds a further step to the above hypothesis, accounting for the stimulation of the axons in the cut nerve. On this hypothesis, it is understood that sympathectomy cures causalgia by removing those fibres, which are fulfilling their known efferent function. It will be noted that this theory is equally applicable to causalgia occurring in partial and in complete lesions, and also to cases of causalgia in amputation stumps.

The possibility of conduction across an artificial synapse has been proved, so it is known that such a mechanism as this stimulation could occur. Granit, Leksell, and Skoglund (1944) have shown in cats that if, in a sectioned nerve, the motor root is stimulated, action currents can be detected in the sensory root; the converse also holds, so that action currents can be obtained from the motor root on stimulation of the sensory root, but in this case the stimulus has to be much stronger. The point where the transmission from motor to sensory, or from sensory to motor, takes place, would seem to be at the cut end of the nerve; this, they call the artificial synapse. Further, they found that it was unnecessary to cut the nerve across; a ligature round the nerve is sufficient to cause an artificial synapse, the nerve not being damaged enough to stop normal distal conduction. The effect was found to be greatest in a freshly damaged region. These facts not only provide a possible basis for Doupe, Cullen and Chance's hypothesis, but also suggest the mechanism of a common feature of the pain of peripheral nerve lesions which was mentioned in the description of the pains—the simultaneous occurrence of an involuntary kicking of the limb and a shoot of pain.

SUMMARY.

(1) Weir Mitchell's original definition of causalgia is restated. It is emphasized what by definition causalgia is, and what may be its occasional accompaniments.

(2) The descriptions of the pains of some cases with lesions of peripheral nerves are given.

(3) The distribution of causalgia and other pains in 160 peripheral nerve lesions is given.

(4) Evidence is brought to show that causalgia may occur in complete lesions of peripheral nerves.

(5) Evidence is brought to show that in peripheral nerve injuries with causalgia, the pain impulses arise in the central end of the damaged nerve, and that they do not arise in the nerve-endings of the region which is felt to be painful.

(6) In order to test Lewis's hypothesis of the genesis of causalgia, 16 cases were investigated. It is shown that this hypothesis does not accord with the facts: because causalgia occurs in amputation stumps; because all possible pathways for nerve impulses interpreted as burning pain can be shown to be absent below the lesion on the nerve-trunk in some cases of causalgia; because in causalgia the skin is not in the erythralgic state.

(7) The role of the sympathetic system in pain conduction is considered. The relevant literature is summarized; observations on personal cases are reported.

(8) The literature on sympathectomy as therapy for some painful conditions is summarized.

(9) It is shown that the following hypotheses of the genesis of causalgia do not accord with the facts: that causalgia is due to vascular stasis; that causalgia is due to local vasoconstriction; that causalgia is due to distal vasodilatation.

(10) It is concluded that the most satisfactory hypothesis is as follows: stimulation of the somatic sensory axons occurs at the site of the lesion on the nerve-trunk; this stimulation is caused by efferent impulses coming down the sympathetic outflow; the site of the lesion forms an artificial synapse, where this stimulation occurs; the pains due to impulses arising at this synapse are referred by the patient to the area of distribution of the sensory nerve.

I wish to thank Professor G. W. Pickering and Mr. W. R. Merrington for help and criticism in the construction of this paper.

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THE FUNCTION OF THE CIRCULUS ARTERIOSUS OF WILLIS.[1]

BY

LAMBERT ROGERS, *Cardiff.*

IT is just three hundred years since Thomas Willis, who was born in Wiltshire in 1620, began to practise at Oxford. There he also began work on his "Cerebri Anatome Nervorumque descriptio et usus" which when published in London in 1664 was the most exact account of the nervous system which had then appeared. In Chapter VIII is the description of the arterial ring at the base of the brain, illustrated by Christopher Wren which perpetuates Willis's name wherever anatomy is taught.

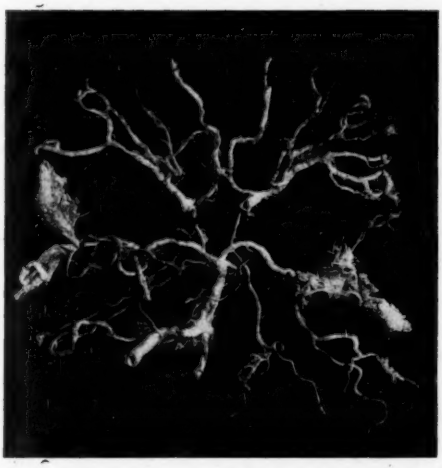

FIG. 1.—A typical "circle" showing the relative sizes of the component vessels in a man aged 48.

Known in this country as the circle of Willis, on the Continent and more precisely as the heptagon or polygon of Willis, the arterial ring has

[1] Based on a communication made to the Anatomical Society of Great Britain and Ireland at Guy's Hospital on November 29, 1946.

for long attracted the attention of anatomists, neurologists and surgeons (fig. 1).

Is the circle a structure peculiar to the blood supply of the brain, having as some maintain the function of a distributor station for equalizing the cerebral blood supply, or is it merely an anastomosis between main arterial trunks?

In an attempt to answer these questions an examination has been made of the circle in a large number of specimens; injection experiments have been carried out on the cadaver; arteriograms have been studied in the living and a working scale model has been constructed on which observations of variations in pressure and flow have been studied.

Variations in the Circle.

Windle (1888), De Vriese (1905), Fawcett and Blackford (1905), Blackburn (1907), Stopford (1916), Busse (1921), Adachi and Hasebe (1928), Godinov (1929), Fetterman and Moran (1941) have studied the circle and recorded its variations. From the large number of observations so recorded it is apparent that it is frequently asymmetrical but only rarely defective. In 100 specimens examined by V. M. Godinov, the circle was complete in 99 and only doubtfully defective in the remaining specimen.

It is true to say then that the circle of Willis is almost always a closed ring, but it may be, and frequently is, an irregular or uneven ring since the communicating arteries vary considerably in size and may be only threadlike connections between the larger vessels.

Functions.

? *An equalizer.*—Some textbooks inform us that by means of the circle of Willis the cerebral circulation is equalized. A friend has informed me that when Professor Starling erected his laboratory at University College, he put a circle of Willis [*sic*] in the basement to make the taps run smoothly! It was compared by another friend with a gas ring, the jets from which would constitute the cerebral arteries.

It is true to say that it is regarded by many as a distributor or equalizing station, a form of circular lake, fed by the carotid and vertebral blood-streams and giving off effluents to the brain.

Willis himself so regarded it for he wrote:

"For in as much as the Carotidick Arteries do communicate between themselves in various places, and are mutually ingrafted; from thence a double benefit results, though of a contrary effect: because by this one and the same means care is taken, both lest the brain should be defrauded of its due watring of the blood,

and also lest it should be overwhelmed by the too impetuous flowing of the swelling stream or torrent. As to the first, lest that should happen, one of the Carotids perhaps being obstructed, the other might supply the provision of both; then, lest the blood rushing with too full a torrent should drown the channels and little Ponds of the brain, the flood is chastised or hindered by an opposite emissary, as it were a Flood-gate, and so is commanded to return its flood, and haste backwards by the same ways, and to run back with an ebbing Tide."

? *An anastomosis.*—It is possible that this conception of equalization and distribution of blood flow is incorrect and that the circle is nothing more than an anastomosis between the main arterial channels constituted by the basilar and carotid arteries and comparable in all respects with other anastomoses between main arterial channels.

(1) Injection Experiments.

In 1912, S. P. Kramer of Cincinnati performed injection experiments on dogs and monkeys using methylene-blue which was injected into the carotid or vertebral arteries just before the animal was sacrificed. It was shown that for the most part the dye remained in the distribution of the artery injected and little or no mingling with the other vessels took place.

(2) Cerebral Arteriography.

Radio-opaque substances in the living such as thorotrast and diotrast produce similar results. If one carotid is injected the carotid system of that side only is outlined; very little of the radio-opaque material leaks into the opposite side or into the posterior cerebral arteries.

(3) Experiments Performed on a Model.

With a working scale model of the circle (fig. 2) it has been possible to verify the results of the injection experiments carried out by Kramer by allowing a coloured solution to flow through one carotid system in the model. It was found that little or no mingling with the other side of the circle occurred. It was also possible to demonstrate the volume and pressure variations in the main vessels distal to the circle after occlusion of a main vessel such as the carotid proximal to it. These variations are such as might be expected to take place if the communicating arteries constitute an anastomosis, rather than part of a distributor station (fig. 3 A, B, C, D, E).

Commentary.

It would appear therefore that the blood leaving the carotid and basilar arteries, for the most part passes directly into the main branches

of these vessels, the communicating arteries merely constituting an anastomosis in their course with but little influence on the stream in the main fairways.

Thus the circle of Willis should not be looked upon as a distributor or equalizing station or booster mechanism for the cerebral blood supply, but merely as an anastomosis. The great value of the anastomosis like all anastomoses must be its potential effect as a shunt capable of opening up and playing an important part should one of the main vessels be occluded.

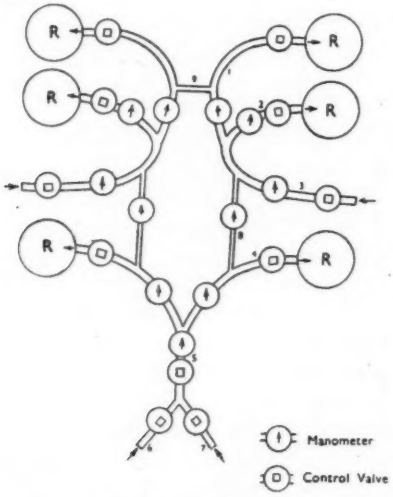

FIG. 2.—Diagrammatic representation of working model of Circle of Willis showing the arrangement and position of manometers, control valves and receptacles (R), for measuring output. 1, anterior cerebral artery; 2, middle cerebral artery; 3, internal carotid artery; 4, posterior cerebral artery; 5, basilar artery; 6 and 7, vertebral arteries; 8, posterior communicating artery; 9, anterior communicating artery.

CAROTID LIGATION.

These conclusions are both supported by and have a bearing on carotid ligation. It is well known that hemiplegia or other cerebral disturbances may sometimes follow carotid occlusion. This should not be so if the circle is a distributor and equalizer, unless in such cases it is defective, i.e. not a closed ring. As it has been shown that it is but rarely defective it is more reasonable to assume that such cases are due to the fact that it is not functioning as an equalizer. As a corollary, carotid ligation per-

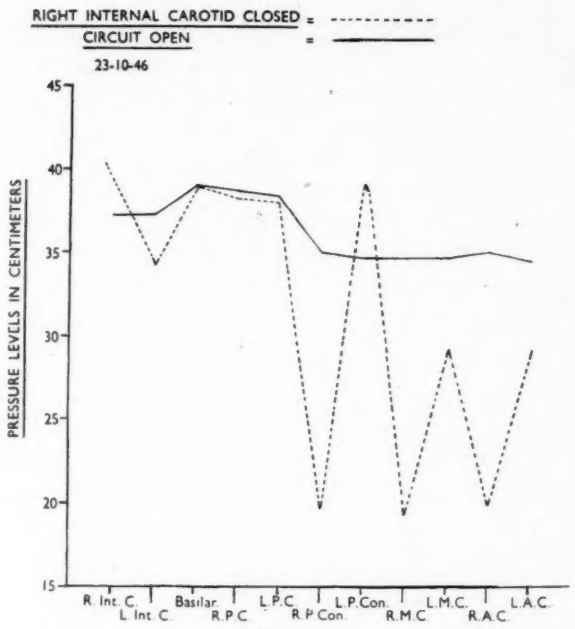
RIGHT INTERNAL CAROTID CLOSED =
CIRCUIT OPEN =
23-10-46
PRESSURE LEVELS IN CENTIMETERS
45
40
35
30
25
20
15
R. Int. C.
L. Int. C.
Basilar.
R.P.C.
L.P.C.
R.P.Con.
L.P.Con.
R.M.C.
L.M.C.
R.A.C.
L.A.C.

FIG. 3A.

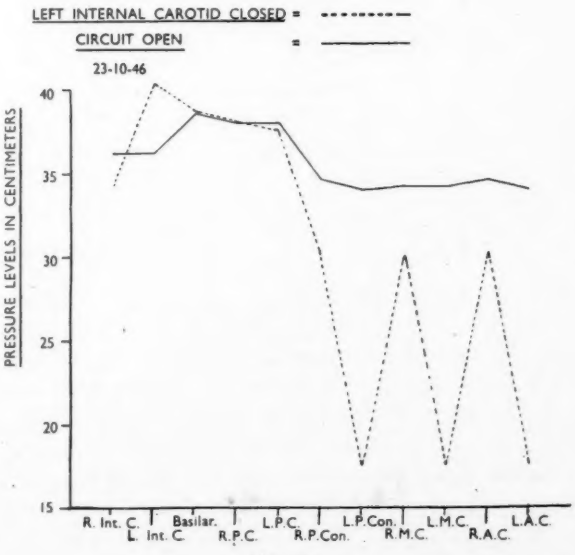
LEFT INTERNAL CAROTID CLOSED =
CIRCUIT OPEN =
23-10-46
PRESSURE LEVELS IN CENTIMETERS
40
35
30
25
20
15
R. Int. C.
L. Int. C.
Basilar.
R.P.C.
L.P.C.
R.P.Con.
L.P.Con.
R.M.C.
L.M.C.
R.A.C.
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FIG. 3B.

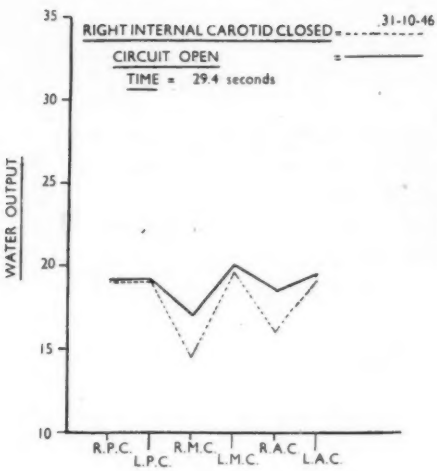

FIG. 3C.

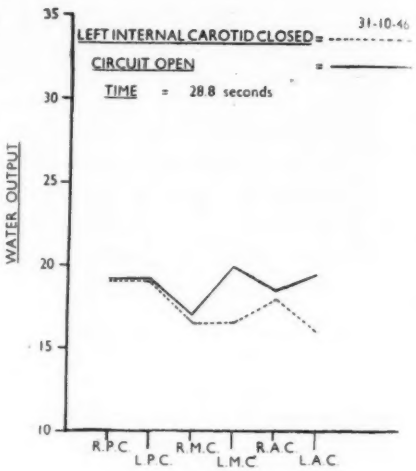

FIG. 3D.

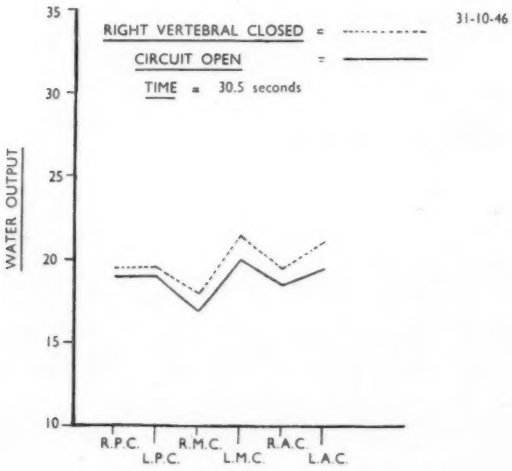

FIG. 3E.

FIG. 3.—A, Pressure changes following closure of right internal carotid; B, Pressure changes following closure of left internal carotid; C, Volume changes following closure of right internal carotid; D, Volume changes following closure of left internal carotid; E, Volume changes following closure of right vertebral.

formed proximal to the circle, e.g. in the neck, should materially influence the blood flow in that part of the vessel distal to the circle and its main branches.

As early as 1902, Victor Horsley ligatured the common carotid for an aneurysm which he had exposed in the middle fossa of the skull and verified by placing a sterilized stethoscope on its surface. His patient was alive and well five years later. In a series of six cases I have successfully practised ligation of the common carotid artery for aneurysm on the intracranial course of the internal carotid or its main branches, either to arrest hæmorrhage when leaking or as a precautionary measure against rupture. Successful reports have also recently appeared from Krayenbuhl (1946) and others and if the patient with an intracranial carotid aneurysm will tolerate occlusion, a question which can be decided by electro-encephalography (Lambert Rogers, 1944), ligature should be performed to arrest leakage and protect the patient from a hæmorrhage which is otherwise liable to be fatal. Such ligature is a true Hunterian operation of distant proximal ligature.

Comparative Anatomy.

The foregoing observations have been made on human subjects in whom the question is of importance in connection with carotid ligation. I have not made observations of the form and functions of the circle in animals but Professor Cave has kindly sent me notes of dissections he has made of the circle in birds (ostrich, emu, crane, penguin, ibis, macaw, &c.). In these he has found the circle deficient, both front and back. He writes that if the condition which he has found is constant for the big avian species the circle cannot be anything more in them than an anastomosis such as my observations would appear to show that it is in man. Professor Wood Jones tells me that in the mammalia he has found the circle best developed in the browsing animals such as the cow.

Summary.

(1) The circle of Willis is a constant, albeit an irregular anastomosis between the vertebral and carotid arterial systems, comparable with anastomoses between main arterial channels elsewhere in the body.

(2) Under physiological conditions it does not permit a mingling of the blood-streams in the main vessels across which it lies.

(3) It should not therefore be regarded as a distributor or equalizing station or booster mechanism for the cerebral blood supply.

(4) Its value is potential rather than actual because like all anastomoses

it provides a by-pass capable of opening up, should one of the main channels across which it lies become obstructed.

(5) Occlusion in the neck of one carotid artery for aneurysm on its intracranial course is effective in reducing blood flow within the aneurysmal sac whether this lie below or above the level of the circle and constitutes a true Hunterian operation of distant proximal ligature.

(6) In a series of cases of leaking cerebral aneurysm causing subarachnoid hæmorrhage, carotid ligation has been performed with success, bleeding being arrested and symptoms relieved.

I am indebted to my friend and colleague, Mr. Arnold Aldis, F.R.C.S., for his help with the construction of the model and the recording of certain of the experiments made with it.

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THE HIPPOCAMPUS AND THE SENSE OF SMELL.
A Review

BY

ALF BRODAL.[1]

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(1) Introduction.

It is a common experience that some old views and statements show a remarkable tendency to outlast the tenability of the original observations on which they were based. The conceptions survive almost like proverbs, and become proclaimed as long-established truths and accepted as such by those who practise in the particular field of knowledge concerned.

Such indeed is the situation to-day in regard to the deep-rooted belief held by neurologists that the hippocampus is an important olfactory "centre." However, some general suspicion of the truth of this credendum seems to be just about to dawn. It appears, therefore, to be worth while to make an attempt to clarify the problem as it stands at present in the light of recent research. This, then, is the aim of this paper. The questions which have to be considered are the following: On what evidence is the assumption founded that the hippocampus has olfactory functions? Does this evidence really justify the conclusions which have been drawn from it, or does more recent evidence make these untenable or dubious? If the hippocampus is not related to the olfactory functions, or at least not exclusively, can any inferences be made concerning its rôle in other

[1] This work was done while the author was holding a Rockefeller Fellowship in the Department of Human Anatomy, Oxford, on leave from the Anatomical Department, University of Oslo, Norway.

functions? It may be assumed that answers to these questions will provide useful information concerning lines of further research in this field.

The statement that the hippocampus or Ammonshorn is related to smell is to be found in nearly every textbook of neurology and anatomy and it is even to be encountered in other works. Thus, to cite the recent monograph of Penfield and Erickson (1941) on "Epilepsy and Cortical Localization," the authors when speaking of olfactory sensations as part of an epileptic discharge (p. 56) state that "it seems to be the hippocampus or cornu Ammonis which must be considered as the site of discharge." On p. 17, not committing themselves too strongly to the olfactory function of the hippocampus itself, they say that "the localization of discharge is doubtless somewhere near the uncinate gyrus."

It is difficult to trace from the literature on what evidence the conception of the essentially olfactory function of the hippocampus was originally founded. No complete review of this historical problem will be attempted here. Some facts which may have played a part in its elaboration will, however, be referred to. First, then, are to be mentioned the findings of comparative anatomists, that the hippocampus in phylogenesis develops in connection with the olfactory portions of the brain, and that it usually shows a strong development in macrosmatic mammals. The inferences drawn from these and other anatomical findings were taken to be supported by Ferrier's report in 1876 that he observed movements of the lip and nostril on electrical stimulation of the hippocampal lobe in monkeys, although he did not precisely indicate the hippocampus itself as the origin of these responses. Some findings made by earlier workers might also be quoted. Finally mention should be made of the description by Hughlings Jackson and Beevor (1890) of the occurrence of subjective olfactory sensations in some types of epileptic fits, later termed *uncinate fits* by Jackson ("uncinate groups of fits"), since these were shown in several cases to occur with lesions in the uncinate gyrus or its neighbourhood (e.g. by Jackson and Beevor, 1890; Jackson and Colman, 1898; and several other papers). In these cases of uncinate fits the uncus has usually been assumed to be the part which, when damaged, provokes the peculiar sensations. As far as is known, no case with a lesion restricted to the hippocampus has yet been shown to be accompanied by uncinate fits, but it appears that by some diffuseness of thought the alleged olfactory functions of the uncus have been attributed to the hippocampus as well. No *decisive* evidence that the hippocampus is concerned in olfaction appears to have been brought forward, although some findings might point to this possibility, as will be mentioned later.

The earlier conclusions concerning the function of the hippocampus were mainly obtained from anatomical studies of normal material. Ferrier's statement from 1876, "The position of the olfactory centre may with great probability be inferred from anatomical considerations alone, apart from actual experiment" (p. 312, 2nd Ed. 1886), to a certain extent is still valid, but only provided that the anatomical methods employed allow a detailed mapping out of the relevant fibre connections. This, however, cannot be achieved by the use of preparations from normal brains or from comparative anatomical studies. It is only by applying experimental methods in the study of fibre connections that definite and conclusive results can be expected. Experimental physiological investigations may give further information, but it should be emphasized that they can be correctly evaluated only when the anatomical structures—nuclei and connections—involved are known. Fortunately, research during more recent years has brought forward some new information concerning the fibre connections in the olfactory system, and it will be the main object of the present paper to consider how the recent findings fit into the conception of the hippocampus as an olfactory region. Although we are here concerned primarily with the hippocampus, it will be necessary for a full comprehension of the problem to deal to some extent also with the connections of certain other parts of the brain, particularly the pathways taken by the olfactory impulses after they have entered the central nervous system. Below, therefore, a brief outline of the principal afferent connections of the olfactory system will be given, which later on will be supplemented with other data of particular relevance to the problem under discussion.

(2) The Afferent Fibres of the Olfactory System.

Most of present-day knowledge concerning the fibre connections of the olfactory system has been derived from studies of normal material of different animal species. Numerous connections have been described and pictured, some of them large and clearly evident, others sparse and difficult to trace. In evaluating the wealth of connections thus laid down in the literature, it should be remembered that the determination of the direction of conduction of a fibre tract is not possible as a rule in normal preparations, and that in the intricate fibre feltwork which is present in most regions, it will always be a matter of conjecture to determine the course of the fibres belonging to one particular system. Mainly for these reasons, it appears wise to abstain from accepting all connections described in normal material as having a real existence. To some extent the same

applies to fibre connections described in cases of malformations in which, in addition, such factors as primary or secondary correlated changes may represent sources of error.[1]

No attempt will be made in this review to enumerate all fibre connections described as belonging to the olfactory system. A complete exposition of these will be found in the textbook by Kappers, Huber and Crosby (1936). Only the more clear-cut connections which have been described in normal material of mammals will be mentioned, leaving out of consideration some of the more indefinite and sparse fibre tracts assumed by some authors to be present. In addition, some experimental findings will be mentioned, and in this section the afferent fibres will be considered (cf. fig. 1).

The fibres leaving the olfactory bulb, where the primary olfactory fibres from the olfactory epithelium of the nasal cavity end, have been studied by various authors in different animals. Restricting the following account mainly to mammals, these fibres have been shown to take their course through the lateral, intermediate and medial olfactory striæ, in a somewhat varying proportion in different species. There appears to be general agreement upon the fact that some of them terminate in the *anterior olfactory nucleus,* which is situated in the posterior part of the olfactory bulb and, more posteriorly, is continued into the cerebral hemisphere.[2] In man this nucleus is relatively small as compared with several other mammals (Crosby and Humphrey, 1941). From the anterior olfactory nucleus other fibres take origin and join the olfactory bulb fibres which pass it without interruption (e.g. Humphrey in the bat, 1936; Young in the rabbit, 1936; Fox in the cat, 1940; Jeserich in the mink, 1945). Fibres from the olfactory bulb, supplemented by those from the anterior olfactory nucleus, continue in a central direction, and have been traced to several destinations, although not equally convincingly to all the structures which have been mentioned. Most authors state that a considerable proportion of these fibres, mainly at least by way of the lateral tract or stria, pass to the *piriform lobe cortex* (O'Leary, 1937; Fox, Gurdjian, 1925; Humphrey, Jeserich, Young, and several earlier authors). By some (e.g. Young in the rabbit) it is stressed that they can be traced to the *anterior* part of the piriform lobe (the piriform lobe corresponds to part

[1] Some aspects of the problem of correlated changes in nervous tissues have recently been discussed at another place (Brodal, 1946).

[2] No specification is made here in regard to whether the fibres relaying in the anterior nucleus pass by the lateral, intermediate or medial stria. For the sake of simplicity, in the following account also, particular details are omitted which appear to be of less importance from a functional point of view.

of the gyrus hippocampi in the human brain, although the nomenclature is not quite consistent on this point, cf. later). Unanimity also seems to exist as concerns the distribution of fibres or collaterals to the *nucleus of the lateral olfactory tract*, which is well developed in many mammals, but according to Crosby and Humphrey (1941) less so in man. This nucleus by most authors is described as closely related to the amygdaloid complex, and fibres have been found to several of the subdivisions of the *amygdaloid nucleus*. Concerning the particular nuclei which receive the fibres from the olfactory bulb or anterior olfactory nucleus, statements are on the whole rather vague. In the bat such fibres have been traced to the medial amygdaloid nucleus and probably connections are established with the cortical nucleus (Humphrey, 1936). In the rabbit Young (1936) was able to follow them to the anterior amygdaloid area, whereas in the cat Fox (1940), while concluding that they reach certain of the amygdaloid nuclei, does not commit himself definitely in which particular elements they terminate.

As regards the contributions of fibres from the olfactory bulb and anterior olfactory nucleus to nuclear groups other than the amygdaloid complex, evidence is on the whole more equivocal. The *tuberculum olfactorium*, corresponding to a part of the anterior perforated space of human anatomy and extending caudally to the *diagonal band of Broca* (Crosby and Humphrey, 1941) is assumed to receive olfactory fibres in the cat (Fox, 1940). Such fibres have also been described in the rat (Gurdjian, 1925), in the rabbit (Young, 1936), and in the opossum (Humphrey, 1936) in accordance with Elliot Smith's original view (1909). However, these fibres appear to be rather scanty, and have not been verified by all observers.

The so-called *septal areas*,[1] which are made up of several minor nuclear groups and have been somewhat variously delimited, are regarded by some as receiving olfactory fibres, although most of their afferent fibres appear to be related to the fornix and stria terminalis systems (*vide infra*). Olfactory fibres from the bulb and anterior olfactory nucleus have been

[1] It should be pointed out that the septal areas are not identical with the septum pellucidum of human anatomy. This contains some nerve cells and is regarded by most authors as representing part of the so-called post-commissural septum, whereas the precommissural septum, developed in front of the anterior commissure, is represented by the parts situated beneath the corpus callosum in the medial wall of the hemisphere, reaching ventrally to the tuberculum olfactorium. The subcallosal gyrus in man forms part of this area. For a discussion of this region from a comparative anatomical point of view, the text of Kappers, Huber and Crosby (1936) should be consulted, as well as Johnston's paper of 1923.

found in the rabbit by Young (1936) to reach the medial septal areas, whereas no mention of such fibres is made by Fox (1940) in his study of the cat. Through a relay in the tuberculum olfactorium, however, olfactory impulses appear to be able to reach the septal nuclei, according to the findings of Young, as well as of Fox and several other authors. This

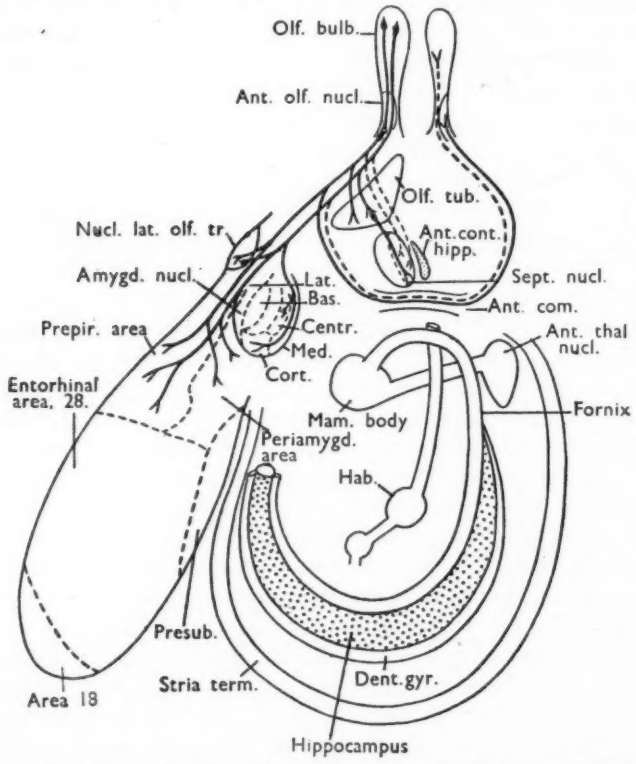

FIG. 1.—A diagram (outlines mainly after Allen, 1940) of the distribution of afferent olfactory fibres from the olfactory bulb and anterior olfactory nucleus. Connections which appear to be definitely established drawn with full lines; certain other connections which appear equivocal are indicated by stippled lines.

tuberculo-septal tract seems to be a rather conspicuous connection as far as can be judged from normal preparations. Additional connections of the septal areas and the amygdaloid complex will be referred to later, as will also some other structures and connections of relevance for the present problem.

In concluding the survey of olfactory fibres from the bulb as they have been mapped by students of normal material, mention should finally be made of the alleged presence of commissural fibres connecting the two olfactory bulbs and the anterior olfactory nuclei by way of the anterior commissure.

The *experimental investigations* of fibre connections within the olfactory system have up to recent years mainly consisted in tracing the olfactory fibres by means of the Marchi method. Only in the last few years has the problem of olfactory connections been tackled by more refined and modern methods. The limitations of the Marchi method are well known, of particular importance being the fact that it permits only the tracing of myelinated fibres, and there is reason to assume that unmyelinated fibre tracts are of some significance in the olfactory system as well as in other fibre systems.

Following lesions of the olfactory bulb some of the pioneers in the study of olfactory connections claimed that commissural connections between the two olfactory bulbs are present (Cajal, Probst, 1901). It appears, however, that their positive findings were due to concomitant injury to the anterior olfactory nucleus. Following such a lesion, all authors agree that commissural fibres degenerate in the anterior commissure, but Young (1941) has recently found in rabbits that no degeneration of commissural fibres occurs if the lesion does not encroach upon the anterior olfactory nucleus.

Centripetal fibres from the olfactory bulb have been followed by the Marchi method by older authors to the nucleus of the lateral olfactory tract and to the piriform cortex (Elliot Smith, 1909; recently verified by Fox and Schmitz, 1943), and by some to the tuberculum olfactorium (thus by Elliot Smith, 1909 in a marsupial) whereas Cajal did not find the latter. On the whole, recent research is in accord with the findings of the older authors.

By leading off from the brain in the hedgehog and recording the changes of electrical potentials following the introduction of odorous substances into the nasal cavity, Adrian (1942) found potential changes in the piriform lobe. In the same way Hasama had earlier (1934) recorded potentials from the olfactory bulb, the olfactory tubercle and the piriform lobe, and in addition from the septal areas. Although physiological in its technique, this method is capable of revealing the anatomical connections underlying the transmission of the impulses, and thus the results may be taken to indicate that olfactory impulses are relayed to the structures mentioned. Fox, McKinley and Magoun (1944) stimulated the olfactory bulb in cats and recorded the ensuing potentials from various parts of the

basal surface of the cortex. They found that potentials were evoked in the olfactory tubercle, the anterior olfactory lobe and in the prepiriform and the piriform cortex (but the caudal superior portion of the latter was not explored). They were not able to detect any potentials in the amygdaloid nuclei, in the septal areas or in the hippocampus, but they point out that these results do not necessarily mean that these parts have no connections with the olfactory system; they may be connected only after a long series of synapses. Rose and Woolsey (1943) with the same method obtained corresponding results, with the exception that the olfactory tubercle did not respond. Allen (1943) also recorded potential responses in the piriform lobe of dogs following application of odours of xylol into the nose as well as when the olfactory bulb was electrically stimulated. Other structures in receipt of olfactory fibres were not investigated.

The most recent study of the afferent olfactory fibre connections is that of Le Gros Clark and Meyer (1947). By means of the silver method described by Glees (1946) these authors traced the terminal degeneration of the fibres following lesions of the olfactory bulb to the nucleus of the lateral olfactory tract, parts of the amygdaloid nucleus (namely the medial, central and cortical), to the tuberculum olfactorium, to the piriform lobe, but only its anterior part, and to the bed nucleus of the stria terminalis. No signs of degenerated terminals were found in the septal areas, or any part of the hippocampal formation. Since the silver method permits the tracing also of unmyelinated as well as myelinated fibres, these findings are particularly important. However, they do not absolutely rule out the possibility of other sites of termination of the olfactory fibres than those mentioned, but at least it can be said that such other connections as might have been overlooked on account of the delicacy of the changes, if they exist, must be sparse and probably functionally insignificant.

In summary it may be said that there is on the whole a fairly good agreement between the recent experimental findings. It appears at present (cf. fig. 1) that fibres from the olfactory bulb, partly with a relay in the anterior olfactory nucleus, are distributed to the following structures: The *nucleus of the lateral olfactory tract*, the *olfactory tubercle*, the *anterior part of the piriform cortex*, and certain of the *nuclei of the amygdaloid complex* (medial, cortical and central). The anterior olfactory nucleus is connected with its fellow on the other side by commissural fibres in the anterior commissure. These conditions are diagrammatically represented in fig. 1, where fibre connections which must be regarded as definitely established are indicated by heavy lines, and some others, which appear less certain, are indicated by stippled lines. Although not verified experimentally, the connection from the olfactory tubercle to the septal

areas is regarded as being present and is drawn in the diagram, whereas the direct connections with the septal areas appear to be somewhat dubious and are indicated by stippling.

(3) The Afferent Fibre Connections of the Hippocampus.

In an attempt to decide whether the hippocampus is concerned in olfactory functions, the question of its afferent connections is of primary importance. Its efferent connections, however, have also to be considered when it comes to evaluate its possible rôle in olfactory functions. The afferent connections of the hippocampus as they have been described in the literature will first be scrutinized, supplemented by some remarks on its structure and evolution, in so far as they may be necessary for a full comprehension of its functional significance.

Mention was made in the preceding section of the fact that some recent authors, working experimentally, were not able to ascertain the existence of fibres passing directly from the olfactory bulb or the anterior olfactory nucleus to the hippocampus (Rose and Woolsey, 1943; Fox, McKinley and Magoun, 1944; Le Gros Clark and Meyer, 1947). However, some students of normal material have maintained that such fibres are present, but as a rule they express themselves very cautiously concerning this point. Fox (1940) states that in the cat fibres from the medial olfactory tract and the anterior olfactory nucleus appear to enter into relation with the *anterior continuation of the hippocampus*.[1] Among others who claim

[1] *The anterior continuation of the hippocampus* is described by most authors as forming an element among the cell groups of the septal areas. It has been identified in acallosal as well as callosal mammals. In callosal mammals it is present as a small group of cells situated beneath the anterior end of the corpus callosum near the median line, and is dorsally continuous with the induseum griseum. (In this Humphrey found all elements of the hippocampal formation to be represented in the bat, namely the hippocampus, gyrus dentatus and subiculum. A similar differentiation has not been possible in higher mammals.) Continuous with the anterior continuation of the hippocampus is the septo-hippocampal nucleus. Both these as well as others of the septal nuclei present some differences in various mammals. They are of interest, however, since Johnston (1913) maintains that the septo-hippocampal nucleus represents a part of the *primordium hippocampi* found in lower vertebrates. Also in human embryos a similar primordium hippocampi is present, and according to Hines (1922) is strictly comparable to the same structure in reptiles. The anterior parts of the primordium hippocampi become separated from the hippocampus proper, when this is displaced caudally, and, where a temporal lobe develops, again ventro-rostrally. It is generally held that the induseum griseum represents what is left of the middle parts of the primordium, although some authors do not agree with this interpretation. The anterior continuation of the hippocampus appears to be a vestige, and from a functional point of view it can scarcely be thought of as an important part of the olfactory system, particularly in mammals.

the presence of such fibres may be mentioned Gurdjian (1925), Young (1936), Humphrey (1936), and Jeserich (1945).

On the whole, the evidence in normal material for fibres from the olfactory bulb and the anterior olfactory nucleus to the hippocampus appears to be indefinite. Such fibres appear to be scanty and have been claimed by most authors to be traced only to the most anterior, precommissural part of the hippocampus, the so-called anterior continuation of the hippocampus. In view of the negative experimental findings it seems permissible to conclude, that *if direct olfacto-hippocampal connections exist at all, they are quantitatively negligible,* the more so when compared with the considerable size of the hippocampus proper.

However, even if direct fibre paths cannot be followed from the olfactory bulb and its nucleus to the hippocampus proper, this does not rule out the possibility that the hippocampus ultimately receives olfactory impulses. There are several possibilities of more indirect pathways, which such impulses might utilize and which must, therefore, be discussed. First and foremost, then, the further connections of the nuclei in receipt of fibres from the olfactory bulb must be considered, and among these the *piriform lobe* presents itself as the region of particular interest.

Cajal (1911 and earlier) opposed the assumption, then current, that the afferent fibres to the hippocampus reached it through the fornix, and showed in studies of normal material that the fornix is, at any rate predominantly, efferent in respect to the hippocampus, a finding which has later been verified by various authors. The afferent fibres to the hippocampus, according to Cajal, are derived from three sources, the most important of these being Cajal's "écorce temporale supérieure ou postérieure," the entorhinal area of the piriform lobe. Cajal's results have later been verified and amplified by Lorente de Nó in painstaking studies of the hippocampus and entorhinal area in various mammals (1933, 1934). According to this author, who appears to be the only one who has studied this problem at all extensively in recent years, the cortico-hippocampal fibres reach the hippocampus through the subiculum. The fibres from the entorhinal area of the piriform lobe are distributed to the dentate gyrus and the hippocampus in their entire posterior parts at least (*vide infra*). Some details of these connections are shown in fig. 2, based on the statements of Lorente de Nó (1934). It will be seen that the fibres arising in the medial part of the entorhinal area are distributed to the prosubiculum only and probably to the first sector (CA1) of the hippocampus (forming together the so-called "alvear path" of Lorente de Nó). The fibres from the lateral parts of the entorhinal area, however, pass as the so-called

"perforant path" to all sectors which are seen in the transverse sections of the hippocampus, except the sector CA4 in the region transitional to the dentate gyrus. The latter is also supplied by these fibres, and probably will be able to transmit the impulses to the sector CA4, since the efferent fibres from the dentate gyrus reach the hippocampus (cf. fig. 2). This

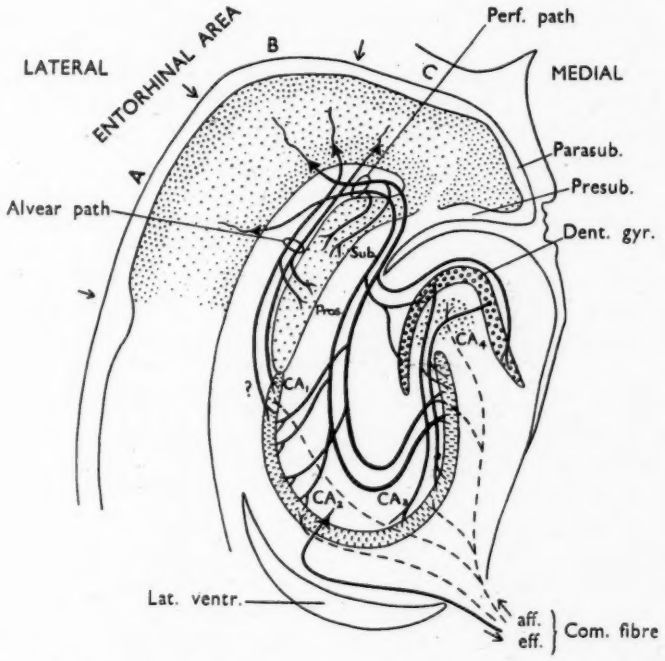

FIG. 2.—A diagram of the arrangement of the fibres from the entorhinal area to the hippocampus and dentate gyrus after Lorente de Nó (1934). The entorhinal area is subdivided into three parts, A, B, C. The four regions of the hippocampus are labelled CA 1-4 respectively. The commissural fibres entering in the fimbria have been included, cf. text.

differential distribution in some way or other is probably related to the structural differences present in the entorhinal area as well as in the hippocampus, differences which have been clearly brought out *inter alia* by Lorente de Nó in his careful studies of the cell types as seen in Golgi and Golgi-Cox preparations. It appears reasonable to assume that the different connections denote differences in function, although the exact significance of these features is still not understood. From a functional point

of view it is worth mentioning that Lorente de Nó discovered the same architectural pattern in the subdivisions of the hippocampus, dentate gyrus and entorhinal area respectively in several species of animals, including monkeys.

As far as is known, experimental investigations of the cortico-hippocampal connections have not yet been undertaken, and ultimate verification of the fibre connections discussed above is thus still lacking. However, there is good reason to believe that the observations of Cajal and Lorente de Nó are essentially correct. Judging from these findings it therefore appears that the main source of olfactory impulses to the hippocampus is to be found in the lateral parts of the entorhinal area, whereas the medial parts are less directly concerned. However, through association fibres (not shown in fig. 2) arising from the prosubiculum, impulses from the medial part of the entorhinal area may also ultimately influence the hippocampus. Furthermore, well-developed intracortical association paths, found by Lorente de Nó in the superficial as well as in a deeper layer of the entorhinal cortex, will presumably be of significance, making possible, *inter alia*, a transmission of impulses from the medial parts of the area to the lateral.[1]

It is a point of particular importance in discussing the alleged olfactory functions of the hippocampus to decide whether the entorhinal area, which thus represents the main source of afferent impulses to the hippocampus, receives olfactory fibres. It was mentioned previously that some authors had found olfactory fibres to the piriform lobe, and it will be necessary to consider more closely if these fibres have been traced to the entorhinal area or only to other parts of the pyriform lobe. This is the more necessary since the designations "piriform lobe" and "piriform cortex" are sometimes employed in a rather indefinite manner. Some remarks concerning the nomenclature will therefore be appropriate.

The term "*piriform lobe*" is usually employed in descriptions of the brains of lower animals only, synonymously with the designation "palæopallium." The piriform lobe is meant to include all cortex between the rhinal fissure (in man continuing more or less clearly the collateral fissure in a rostral direction) and the hippocampal formation (hippocampus and dentate gyrus and subiculum). The subiculum is commonly regarded as a transitional zone between the piriform lobe and the hippocampal formation, and can be further subdivided (cf. fig. 2). Some (e.g. Rose) group the

[1] Lorente de Nó was not able to decide whether the axons of the pyramidal cells of the subiculum enter the fimbria or end in CA1 or CA2.

subiculum with the hippocampus, the presubiculum with the piriform cortex.

The *cortex of the piriform lobe* has been subdivided by several authors into different areas (*see* figs. 1 and 5). On the whole these different attempts at subdivision are in fairly good accord. The most posterior or caudal part of the piriform lobe is the *entorhinal area,* area 28 according to Brodmann's nomenclature. In man it covers most of the hippocampal gyrus, except its most posterior part. The area entorhinalis corresponds to what Cajal called "écorce temporale supérieure ou postérieure." (Lorente de Nó includes in what he calls area entorhinalis also the area perirhinalis, area 35 of Brodmann.) The entorhinal area, as will be seen, does not comprise the entire piriform lobe cortex.

In front of the entorhinal area are found the *periamygdaloid* and the *prepiriform* areas. Of these the latter is usually described as reaching for a considerable distance in the rostral direction along the rhinal fissure and the lateral olfactory tract, extending in the rabbit and the rat almost to the olfactory bulb (*see* e.g. Rose, 1936, and Krieg, 1946 resp. and fig. 5). The cortex of the piriform type thus clearly extends further rostrally than does the macroscopical formation which has given rise to the designation piriform lobe. This is reflected in the designation prepiriform area (Rose) and in the frequent application of the term prepiriform or anterior piriform in macroscopical descriptions.

Returning now to the olfactory fibres entering the piriform lobe, it appears that the emphatic statement by Cajal (1911) that his "écorce temporale supérieure ou postérieure" (the area entorhinalis) does not receive olfactory fibres is still valid. Mention was made previously that in normal preparations from the rabbit Young (1936) found olfactory fibres to the anterior part of the piriform cortex. Although he does not mention the particular cortical areas, there can be little doubt from the description that the fibres were not followed as far as the entorhinal area. The same applies to the description of these fibres in the bat by Humphrey (1936), and from Fox's paper (1940) it is seen that in the cat the olfactory fibres spread over the piriform lobe cortex. But it is not mentioned more precisely how far caudally they reach, and from the figures it cannot be seen that they appear at a level where the entorhinal area should be present. O'Leary (1937) in his study was only concerned with cortex belonging to the periamygdaloid and prepiriform areas. With reference to the literature up to 1936 Kappers, Huber and Crosby do not specify olfactory connections to a particular part of the piriform lobe, although fibres to this have been found by several earlier authors.

It thus appears that positive evidence of the termination of olfactory fibres in the entorhinal area is lacking, at least from studies of normal material. This seems to be in accord with the results of some experimental findings, even if some experimentators have not indicated exactly with which part of the macroscopical piriform lobe they were concerned. From Allen's figure (1943) it appears that his electrodes can scarcely have been placed in the entorhinal area. Hasama (1934) gives two figures showing the areas from which he was able to record potentials in the rabbit. From a comparison of his drawings with Rose's map of the cytoarchitectonics it is seen that the entorhinal area did not respond, or at least this can only have been the case with the extreme oral part of it. Fox, McKinley and Magoun (1944) mention that they did not investigate the "écorce temporale supérieure ou postérieure." However, they draw attention to a fact of some interest. They noticed that the potentials evoked in more posterior parts of the piriform lobe were smaller than those from the anterior parts, and assume on this basis that if potentials can be obtained from the "écorce temporale supérieure ou postérieure" after stimulation of the bulb, they will be small. Finally Le Gros Clark and Meyer (1947) were not able certainly to trace the olfactory fibres to the entorhinal area. The only investigators who have reached other conclusions are Rose and Woolsey (1943). They obtained potentials also from the entorhinal area when the olfactory bulb was stimulated in cats. However, the responses were only small.

In view of the findings summarized above, it appears *permissible to assume that olfactory fibres from the bulb probably do not reach the area entorhinalis, but are distributed to the more anterior parts of the piriform lobe only, the prepiriform and periamygdaloid areas.* If this assumption is correct, however, as is probable, it means that olfactory impulses can only be transmitted to the hippocampus through a relay in the piriform cortex. Probably association fibres from the prepiriform and periamygdaloid areas to the entorhinal area (*see* e.g. Cajal, 1911) will be able to establish a connection, but clearly this places the hippocampus in an entirely different position in regard to olfactory function than if direct fibres had been present to the entorhinal area. The functional aspects will be treated more fully below. First, however, other possible sources of olfactory impulses to the hippocampus should be discussed.

Cajal, as was mentioned, enumerated three afferent pathways to the hippocampus. Apart from the fibres from the entorhinal area, discussed above, he found an afferent path entering through the cingulum and a third contribution through the supracallosal striæ. Lorente de Nó sub-

stantiated this, and maintained that the fibres from the three different sources do not mix when they enter the hippocampus, but that each component is distributed to a particular part only of the Ammonshorn, with a certain amount of overlapping. This differential distribution is indicated in the diagram of fig. 3, from which it will be seen that the

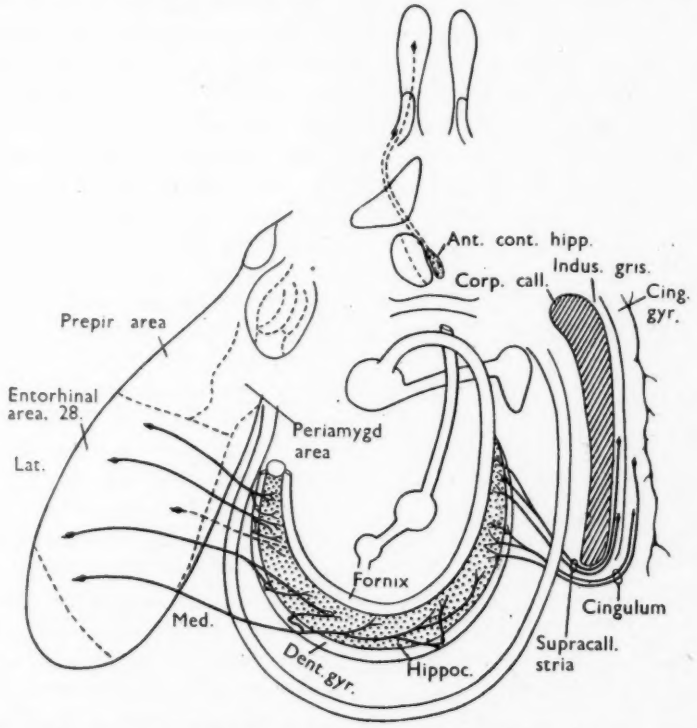

FIG. 3.—A diagram of the afferent fibres to the hippocampus. Only connections which appear to be definitely established are shown. The afferent fibres to the anterior continuation of the hippocampus are stippled, since they appear to be sparse. The commissural fibres are omitted. The differential distribution of the hippocampal afferents is shown as stated by Lorente de Nó, cf. text.

fibres arriving through the supracallosal striæ supply the uppermost portion, those passing through the cingulum the middle portion, whereas the largest contingent from the entorhinal area is distributed to the major, lower, part of the hippocampus. In his paper from 1934 Lorente de Nó is concerned only with the fibres from the entorhinal area, and states

that the other components are to be described later. Unfortunately, however, these studies appear not to have been published, and we have to content ourselves with his preliminary statement on this point. Of even more interest for the present problem, is the origin of these fibres. Do they convey olfactory impulses to the hippocampus or not?

Very little is to be found in the literature concerning this question, apart from Cajal's description. Cajal, however, expresses himself very definitely, and states that the fibres entering through the *cingulum* are derived from the posterior parts of the cingular gyrus only. Most important among these are fibres going to the subiculum and Ammon's horn. His statement is in accord with the experimental findings of Probst (1903) that, following lesions of the cingular gyrus, degenerated fibres can be traced backwards from the posterior part of the gyrus only, and that lesions in the anterior part of the gyrus result in degenerated fibres passing in a rostral direction.

The fibres entering the hippocampus from the *supracallosal striæ*[1] according to Cajal are derived from the nerve cells in the induseum griseum, covering the corpus callosum on its dorsal surface. They take origin predominantly in the posterior parts of the induseum, and enter the dentate gyrus, whereas some can be followed also to the hippocampus itself. If Cajal's observations are valid, as there is reason to believe, it can scarcely be assumed that the two groups of fibres under consideration, are concerned in transmitting olfactory impulses to the hippocampus, since neither the cingular gyrus nor the induseum griseum have been shown conclusively to receive olfactory fibres. Although some fibres have been described in normal material as passing between the supracallosal striæ and the fornix (partly by penetrating the corpus callosum) and being related to the septal areas, their direction is now generally assumed to be efferent in respect to the hippocampus (*see* e.g. Fox, 1940; Young, 1936). And in spite of the findings by Crosby (1917) in the alligator that the medial septal nucleus is a station for ascending impulses to the hippocampus, the actual termination of ascending fibres from the septal nuclei in the hippocampus appears not to have been ascertained, nor does this seem to have been done in mammals. Even if such connections should be verified, they will certainly be scanty and probably of limited functional importance.

It remains to see if connections are present between other structures receiving fibres from the olfactory bulb and the anterior olfactory nucleus

[1] The medial longitudinal stria (Lancisi) and the lateral (tænia tecta) are treated collectively, overlooking smaller differences.

and the hippocampus. It may be briefly stated, that, excepting some small and indefinite fibre bundles described by some authors, conclusive evidence appears to be lacking of contributions to the hippocampus proper from the amygdaloid nuclei, the nucleus of the lateral olfactory tract and the tuberculum olfactorium. The contributions from the septal areas have been treated above. As mentioned previously there seems to be some doubt whether olfactory fibres from the bulb reach the septal nuclei, even if fibres from the tuberculum olfactorium may transmit olfactory impressions to the septum.

In order to complete the enumeration of afferent connections to the hippocampus, the commissural fibres between the two hippocampi, passing in the posterior hippocampal commissure or psalterium, should be mentioned. Such commissural fibres have been described by numerous authors, and are generally believed to interconnect the two hippocampi, although the possibility is not excluded that some of them at least are fibres derived from the entorhinal area which by way of the commissure reach the contralateral hippocampus. Fig. 3 illustrates the main afferent connections of the hippocampus.

Summarizing it may be stated that there can be little doubt that the overwhelming majority of afferent fibres to the hippocampus come from the entorhinal area, probably mainly its lateral part (cf. figs. 2 and 3). Some of them pass to the hippocampus directly, others go to the dentate gyrus, from which the impulses are transmitted to the hippocampus. The entorhinal area, however, probably does not receive direct olfactory fibres. The details concerning the subiculum and its neighbouring regions are not entirely clear, but these structures appear to be intermediate stations between the entorhinal area and the hippocampus. There appears to be no pathway through which the hippocampus can be influenced directly by olfactory impulses. The afferent fibres reaching it through the supracallosal striæ and the cingulum are probably not related directly to olfactory functions.

(4) The Efferent Fibre Connections of the Hippocampus.

There seems to be general agreement on the issue that *the fornix* represents the main, and probably the only, efferent pathway from the hippocampus. This fibre system has been rather extensively studied from the time of the old anatomists up to recent years, being a macroscopically distinct and peculiar structure of the brain. It will be appropriate to consider the fornix somewhat more closely as a knowledge of some details will be of importance in the subsequent analysis of the functional importance of the hippocampus.

The most recent study of the fornix system appears to be that of Allen from 1944 (which the reader should consult for references to earlier literature on the fornix). From the findings in dogs after experimental transection of the fornix Allen concluded that the fornix fibres arise from all the pyramidal cells of the hippocampus and from isolated pyramidal cells of the polymorph layer of the dentate gyrus, since these cells presented chromatolysis. On the other hand, no degenerated fibres could be ascertained in Marchi preparations passing *to* the hippocampus after such transections. This is in accordance with the observations of several other authors. It seems at present justified to state that the fornix is exclusively efferent in respect to the hippocampus. According to Lorente de Nó (1934) the prosubiculum sends fibres to the fornix, whereas it is not known if the subiculum contributes.

The major part of the fornix fibres pass to the mammillary body, as is learnt from Allen's as well as from several earlier papers. Some particulars will be mentioned in the next section. In addition, however, smaller contingents of fibres are distributed to other structures, and are shown in the diagram in fig. 4.

Overlooking the detailed course of the various components of the fornix fibres[1], the terminations to which fornix fibres have been traced in normal material are the following: *The septal nuclei, the preoptic region, the habenula, the hypothalamus* (*see* fig. 4). These findings have been made rather consistently in normal material, e.g. of the bat (Humphrey, 1936), of the rabbit (Young, 1936) and the cat (Fox, 1940). Concerning details there are some differences of opinion between these authors. Thus Young maintains that some fibres continue from the preoptic region in a caudal direction in the medial fore-brain bundle, whereas Humphrey is in doubt concerning this. Most of the fibres to the hypothalamus are said to be distributed to its anterior parts (Humphrey), and the fibres to the habenula, which leave the fornix to join the stria medullaris, are assumed to reach mainly the medial habenular nucleus. Some authors find fibres to the nucleus of the diagonal band. Some of these connections have been also

[1] Although the majority of the fornix fibres pursue a course beneath the corpus callosum (the fornix longus of older authors) some are found in callosal mammals which pass on the dorsal surface of the corpus callosum, in the striæ of Lancisi. Some of these break through the anterior part of the corpus callosum, and together with fibres from the main fornix are distributed in front of the anterior commissure and therefore designated as precommissural. Other fornix fibres, mainly derived from the main bundle of the fornix, but supplemented by fibres breaking through the corpus callosum, constitute the post-commissural fornix, which distributes caudally to the anterior commissure, mainly to the mammillary body.

ascertained experimentally. Thus Fox (1943) traced some fibres of the (precommissural) fornix from the inferior portion of the hippocampus to the lateral septal nucleus in Marchi preparations in the cat, and Allen (1944) ascertained some fornix fibres terminating in the hypothalamus in front of the mammillary body in the dog. However, as pointed out e.g. by Fox (1940), most of the fibres given off by the fornix to the various nuclei mentioned are unmyelinated, and thus will escape recognition in Marchi preparations. The presence of fornix fibres to the medial habenular nucleus also in man has recently been stressed by Marburg (1944) in studies of normal material and cases of malformations.

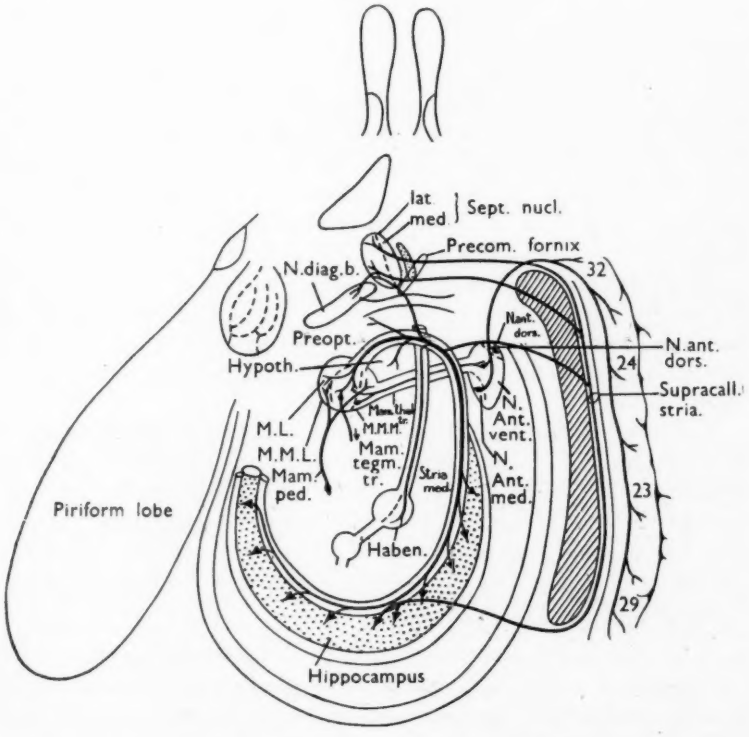

FIG. 4.—A diagram of the efferent connections of the hippocampus, and of the connections from the mammillary body via the anterior nucleus of thalamus to the cingular gyrus, the areas of which are indicated by numbers referring to Brodmann's map, cf. text. M.L.: Lateral mammillary nucleus. M.M.L. and M.M.M.: Lateral and medial part of medial mammillary nucleus respectively.

Apart from the connections of the fornix described above, the presence of *commissural hippocampal fibres* should be recalled. Most of these appear to cross in the ventral hippocampal commissure (commissura fornicis or ventral psalterium) and pass to the hippocampus of the other side. Their exact termination has, however, not been determined experimentally. In descriptions of normal material it has been found that a certain proportion of the fibres of the precommissural fornix (cf. footnote p. 196) cross the mid-line anterior to the anterior commissure. Although the proportion of crossed to uncrossed fornix fibres has not been determined, it appears clear that the hippocampus of either side is able to influence the septal, pre-optic and probably hypothalamic areas on both sides. The mammillary body, however, and presumably the habenula, appear to be supplied mainly by fibres from the homolateral fornix, although the possibility remains open that some fibres may be derived from the opposite hippocampus and cross in the hippocampal commissure. It remains for future research to decide whether the relation between the mammillary body and the hippocampus is purely homolateral. If this should be the case, another point will be added to those which tend to show that the hippocampal fibres to the mammillary body are to a certain extent functionally different from those to the septal, hypothalamic, pre-optic and habenular nuclei. Another question of interest in this connection, which is still open, is the origin of the fibres to the different terminal areas. Do they arise from definite parts of the hippocampus, or are all parts of the hippocampus concerned in the supply of the mammillary body as well as the other areas?

Summarizing the efferent connections of the hippocampus, it appears that the fornix is the sole efferent tract from this structure. The largest proportion of its fibres are distributed to the mammillary body, mainly at least homolaterally. Other fibres pass to the hypothalamus, the septal area, the pre-optic area and the habenula (medial nucleus). These fibres are partly crossed. Commissural fibres probably interconnect the two hippocampi.

(5) Certain Other Relevant Fibre Connections.

Before an attempt can be made to evaluate the rôle of the hippocampus in olfaction, it will be necessary to know the pathways taken by the hippocampal impulses after they have been distributed to the terminal nuclei of the fornix considered above. Although we are still far from having a satisfactory knowledge of these connections, certain of them are fairly well known. This holds good particularly for *the mammillary body* and its connections.

In mammals the mammillary body is made up of different nuclei, which have been designated somewhat differently by various authors. According to the nomenclature applied by Ingram (1940) there is a large small-celled medial nucleus (which has been further subdivided in several species of mammals), laterally a large-celled lateral nucleus is found (called the nucleus intercalatus by Le Gros Clark, 1938). In addition a nucleus intercalatus (small-celled) and smaller groups (premammillary and supramammillary nuclei) can be distinguished in most forms. There seems to be agreement that the bulk of the fornix fibres terminate in the medial nucleus, particularly its lateral part, and probably a smaller contingent in the large-celled lateral nucleus (Allen, 1944). According to Allen, as well as Le Gros Clark (1932), there is no evidence that fornix fibres cross the mid-line before they terminate in the mammillary nuclei. Although the fornix is by far the most important fibre system entering the mammillary body, it may be well to mention that another afferent system, probably more important in lower animals than in man, is the *mammillary peduncle*. Long recognized to be, at least predominantly, an ascending system, this tract has recently been assumed by Fox (1941) to arise partly in the so-called ventral tegmental nucleus (at the level of the red nucleus) and to terminate in the lateral and in the anterior end of the medial mammillary nuclei. (In a later paper, however, Fox and Schmitz (1944) assume this nucleus to be part of the substantia nigra and to distribute ascending fibres in the cerebral peduncle). A possible significance of this will be considered below.

The hippocampal impulses reaching the medial mammillary nucleus are conveyed mainly to the anterior nucleus of the thalamus; to a lesser extent they appear to pass caudally by way of the mammillo-tegmental tract, whose exact termination is unknown but probably is somewhere in the brain-stem. Probably some of the fibres in this tract originate in the lateral, large-celled, mammillary nucleus. Whereas the mammillo-tegmental tract is thus clearly a fibre system conveying impulses from the hippocampus in a caudal direction, the mammillo-thalamic tract is just as clearly an ascending fibre system. According to Le Gros Clark (1932) its fibres in the rat are distributed to all of the three elements of the anterior thalamic nucleus, although predominantly to the antero-ventral nucleus in higher mammals. This is of interest since this part of the anterior nuclear complex shows a progressive development in the phylogenetic ascent of mammals. In the macaque the antero-medial and antero-dorsal nuclei are small (Walker, 1938*a*, and other authors), in the chimpanzee they are still more reduced (Walker, 1938*b*) and in man they are present

only as traces (Sheps, 1945) or are even said not to be developed at all (Toncray and Krieg, 1946). On the other hand the antero-ventral nucleus increases and in man makes up practically the entire anterior nucleus, protruding into the lateral ventricle as the anterior tubercle of the thalamus. It should be mentioned that this progressive development of the antero-ventral nucleus occurs simultaneously with a corresponding increase of the medial mammillary nucleus and the mammillo-thalamic tract, an anatomical feature of some interest for the problem under consideration (*vide infra*). The presence of some descending, thalamo-mammillary fibres in the tract is also of interest. According to Le Gros Clark (1932) these end in the medial mammillary nucleus.

The efferent connections from the anterior nucleus have been shown to be with the cerebral cortex (*see* fig. 4). Following hemidecortication in monkeys (Walker, 1935) and opossum (Bodian, 1942), all groups of the anterior nucleus degenerate. Several authors have studied these connections experimentally. They all agree that the main connection is from the antero-ventral nucleus to the cingular gyrus (Le Gros Clark, 1932, Waller, 1934, and Lashley, 1941, in the rat; Le Gros Clark and Boggon, 1933, in the cat; Walker, 1936, assumes the same to be the case in the monkey). Unfortunately, the parts of the cerebral cortex involved in the lesions, or to which the degenerating fibres have been traced, are not always indicated by reference to their cytoarchitectural features. As far as can be seen the cingular areas (23 and 24) appear to receive the bulk at least of the fibres from the antero-ventral nucleus. That the retrosplenial area (area 29) also receives fibres is maintained by several authors, some of which state that this part is supplied by the antero-dorsal nucleus (Waller, 1934; Lashley, 1941; Bodian, 1942). The anterior part of the cingular gyrus, however, also receives fibres, and it appears that these pass from the antero-medial nucleus (Bodian, 1942; Lashley, 1942) and terminate in what is designated as area prelimbica (area 32) according to the findings of Le Gros Clark and Boggon. Waller (1934, 1937) likewise assumes this to be the case in rats and cats, and the region shown by Bodian (1942) to receive fibres from the antero-medial nucleus in the opossum might well be the corresponding area in this animal. There appears to be a clear spatial relationship between the anterior thalamic nucleus and its cortical projection area according to Walker's findings in macaques (1936). In the opossum Bodian found evidence that the lateral parts of the nuclei are projected more caudally than the medial parts, a finding in agreement with the observations of Le Gros Clark and Boggon.

The cortico-thalamic projections from the cingular gyrus will be considered later.

It will be seen, from the brief account given above, that there can be little doubt that a large proportion of the efferent impulses from the hippocampus are finally transmitted to the cerebral cortex, first and foremost, at least, to the cingular gyrus. On the whole this system appears to be rather simply organized, and, in spite of certain questions still unsolved, is fairly well known. Far less clear-cut and less thoroughly known are the routes taken by the other efferent fibres from the mammillary body. The unsatisfactory knowledge concerning the descending pathway provided for by the mammillo-tegmental tract was referred to above. Even less clear is the situation with regard to the hippocampal fibres distributed to the hypothalamus and the septal and pre-optic areas. The fibre connections of these areas are extremely complex, which indeed is not surprising in view of their structural complexity, each of them being composed of several smaller nuclear groups which to some extent differ in structure. What is known of fibre connections in these regions has mainly been achieved by minute studies of normal material, and consequently leaves much to be desired in regard to definite evidence. No attempt will be made here to review the details of the fibre connections of these regions as they have been described in the literature. Some remarks on principal features will suffice, the more so since the details in the distribution of the fornix fibres are not sufficiently clear.[1]

The best known of the *efferent hypothalamic* pathways appear to be the connections with the *hypophysis*. These fibres take origin predominantly from the supra-optic nucleus and partly from the paraventricular nucleus and are distributed mainly to the neuro-hypophysis. From other hypothalamic nuclei fibres join the *medial fore-brain bundle*, primarily an olfactory structure, and appear to pass caudally in the brain-stem. Although the ultimate termination of these descending hypothalamic tracts and their details have not been established, it appears from physiological experiments with transection of the brain-stem and spinal cord at different levels that they descend throughout the cord. These descending connections are presumably of high importance. The mammillo-tegmental tract appears to belong to the same category. A hypothalamo-cortical pathway from the hypothalamus, apart from the mammillo-thalamic tract and its continuation to the cingular gyrus, is provided for by the hypothalamic connections with the dorsomedial nucleus of the thalamus which is projected on the frontal lobe cortex. In addition there appear to be contributions from the hypothalamus to certain structures of the extrapyramidal system.

[1] A more complete account of the hypothalamic connections is to be found, e.g. in Le Gros Clark *et al.* (1938) and in Ingram's paper of 1940.

Judging from the fibre connections, it appears that the hippocampal impulses distributed to the hypothalamus, and probably those to the pre-optic area as well, may be integrated in the hypothalamus with other impulses. In this way they will be able to play a rôle in the autonomic influences on lower functional levels as well as on the cerebral cortex. Clearly, however, the relatively small proportion of these fibres does not make it likely that the hippocampus is of major importance for hypothalamic functions, at least not in higher mammals and man.

The hippocampal fibres ending in the septal area, although indirectly capable of transmitting impulses to the hypothalamus, appear to enter into relation predominantly with olfactory structures. The septal area has been touched upon above, and it will be appropriate to consider this area in connection with a brief summary of the olfactory connections not related to the hippocampus and not yet mentioned, since these will have to be referred to later on when the functional aspect of the hippocampus is discussed. Only a brief summary of current conceptions will be given.

The septal areas are assumed on the basis of findings in normal preparations to contribute fibres to the medial forebrain bundle and to the nucleus of the diagonal band of Broca. Partly relayed in this nucleus, fibres are said to pass to the amygdaloid nuclei. Other fibres from the septal nuclei partake in the formation of the *stria medullaris*, into which have been traced fibres from several other regions as well. Among these may be mentioned fibres from the amygdaloid nuclei, from the hypothalamus and pre-optic area, from the cortex of the piriform lobe, the nucleus of the lateral olfactory tract, and fibres from the stria terminalis. (The last named, however, were not verified experimentally in the cat by Fox, 1943.) That some fibres from the hippocampus leave the fornix and join the stria medullaris was mentioned previously. Concerning details much is still unsettled, but it appears to be generally agreed that all fibres of the medullary stria pass in a rostro-caudal direction and terminate in the habenula, partly after crossing in the habenular commissure. Although possibly efferent fibres may pass from the habenular nuclei to the thalamus and the tectum, the bulk of efferent fibres course as the *fasciculus retroflexus* to the interpeduncular nucleus, from where impulses are probably transmitted to the dorsal tegmental nucleus. From this the *dorsal longitudinal fasciculus* is believed to take origin. It is probable that fibres from the mammillo-tegmental tract also end in this nucleus. The stria medullaris thus appears to be, predominantly at least, a link in a descending pathway, capable of transmitting olfactory impulses, or olfactory impulses integrated with others, in a caudal direction to lower centres of the brain-stem.

The other conspicuous tract in the olfactory system is the *stria terminalis*. Most of its fibres at least appear to take origin from the amygdaloid nuclei, and according to the recent experimental investigations by Fox (1943) mainly from the basal amygdaloid nucleus. Investigators working on normal material have claimed their origin from the medial, cortical and central nucleus as well (*see* e.g. Young, 1936; Fox, 1940; Jeserich, 1945). Smaller contributions have been described from the nucleus of the lateral olfactory tract, and some other structures. In accordance

with the prevailing conception of the direction of fibres in the terminal stria, Fox (1943) found in Marchi studies that, following interruption of the stria, degeneration could only be followed in a rostral direction, which strongly indicates that the stria is purely efferent in respect to the amygdaloid complex. Its fibres were found to be distributed to the septum, the pre-optic area and the hypothalamus, mainly near the paraventricular nucleus. The fibres alleged to join the stria medullaris were not ascertained, as already mentioned. It appears that the stria terminalis is mainly a pathway for olfactory impulses from the amygdaloid nuclei to the basal centres mentioned, from which the impulses may be transmitted to the brain-stem by means of the medial fore-brain bundle (and via the stria medullaris system?), and furthermore there appear to be connections from the septal nuclei to the basal ganglia. Other interconnections between the olfactory fibre tracts and extrapyramidal structures also appear to be present, indicating a possible influence of olfactory impressions on the extrapyramidal system.

The *anterior commissure* should finally be referred to again. A phylogenetically old structure, this is commonly assumed to represent mainly a commissural connection between olfactory structures on the two sides. Thus mention has been made of fibres interconnecting the two olfactory bulbs or at least the two anterior olfactory nuclei. Other commissural fibres have been described as arising from the amygdaloid nuclei, the piriform cortex, the nucleus of the lateral olfactory tract, and the olfactory tubercle. However, it appears not to have been proved that all of these fibres are really commissural. Some of them may be fibres which soon after crossing in the commissure leave this to reach their place of destination. It is worth mentioning in this connection that Fox and Schmitz (1943) were unable to follow the commissural component of the stria terminalis, generally identified in normal preparations, across the commissure. This may indicate an arrangement as that just mentioned, although other explanations may also be given.

Summarizing the principal features of the preceding section (cf. fig. 4) it may be said that the greatest proportion of impulses arising in the hippocampus reach the mammillary body. From this they are transmitted *via* the anterior thalamic nucleus (mainly the antero-ventral nucleus) to the cortex of the cingular gyrus. The medial mammillary nucleus, the antero-ventral thalamic nucleus, and the mammillo-thalamic tract interconnecting them, undergo a progressive development in higher mammals. Other hippocampal impulses reaching the hypothalamus, the septal and pre-optic areas, are probably engaged in subcortical mechanisms predominantly, being able to discharge caudally by different pathways. The hypothalamo-cortical projection to the frontal lobe via the dorso-medial thalamic nucleus should be borne in mind. The stria medullaris appears to be mainly a descending pathway to the brain-stem, originating *inter alia* from the septal nuclei and hypothalamus and receiving also some fibres from the hippocampus and possibly fibres from the amygdaloid nuclei and piriform cortex. The stria terminalis is to be considered as the main efferent connection of the amygdaloid area, transmitting olfactory impulses to the hypothalamus, septum and pre-optic region.

(6) The Relation of the Hippocampus to Smell in the Light of Recent Research.

On the basis of the anatomical features described in the preceding sections of this paper, an attempt will now be made to analyse whether the anatomical connections, so far as they are known, favour the concept that the hippocampus is related to smell. In addition some relevant physiological findings will be mentioned.

Starting, then, with a consideration of the *hippocampus itself,* it should be realized that from a morphological point of view, this part of the brain must be considered a clear-cut example of a purely *effectory structure.* Although scattered cells are present in the adjoining fibre layers (the striatum oriens and lacunosum) the overwhelming majority of its cells are found arranged as the dense layer of pyramidal cells (Ammon's pyramids), richly endowed with dendrites penetrating the deeper and more superficial fibre layers. The presence of this compact layer of large pyramidal cells, cells of the type recognized in other places as effectory or motor, strongly suggests that the hippocampus is primarily an effectory structure. This conclusion is made even more probable when it is considered that the axons from all the pyramidal cells, and from several of the scattered cells in the other layers as well, join to form a compact efferent fibre bundle, the fornix, which travels as a clear-cut pathway for a long distance through the brain. *From a morphological point of view there is no reason to assume that the hippocampus is to any considerable extent concerned in receptory and associative functions,* be these olfactory or of other kinds. The dentate gyrus is often considered as the receptive part of the hippocampal formation, and it appears, as has been seen, that some of the impulses destined to reach the hippocampus do so by passing the cells of the dentate gyrus. But clearly a considerable part of the afferent impulses to the hippocampus reach this without a relay in the dentate gyrus (cf. fig. 2). Although the significance of the dentate gyrus is not entirely clear, its interpolation between the afferent fibres and the hippocampus does not make untenable the contention that the hippocampus proper is an effectory structure. The rôle of the subiculum and its various sub-areas is also not clearly understood, but this need not concern us here.

The determination of the effectory nature of the hippocampus, of course, tells us little of its possible relation to the sense of smell. In order to obtain information on this point we have to turn to the afferent connections, if conclusions are to be drawn on the basis of structural features. From an analysis of data available from the literature, discussed above, it appears that direct olfactory impulses are probably not transmitted to

the hippocampus. The fibres from the olfactory bulb (and anterior olfactory nucleus) appear to reach the prepiriform and peri-amygdaloid areas of the piriform lobe only. The fibres from the piriform lobe to the hippocampus are probably derived exclusively from its posterior parts, the entorhinal area. The smaller afferent contributions to the hippocampus, reaching it from the posterior part of the cingular gyrus through the cingulum, and the fibres arriving through the supracallosal striæ, can scarcely be assumed to convey olfactory impulses. It thus appears that the *primary olfactory cortex* is to be found in the *prepiriform and peri-amygdaloid areas.* These areas belong to the allocortex of *O.Vogt* or the heterogenetic cortex of Brodmann[1] and a comparison based on the pattern of stratification therefore cannot be made with areas of the neocortex. On account of this, no particular importance can be ascribed to the lack of cytoarchitectural similarity between these areas and the other primary receptive cortical areas which are endowed with granular cortex (koniocortex). A structural feature which may perhaps, at least in part, be responsible for the different structure of the primary olfactory cortex as compared with the optic, acoustic and somæsthetic cortex, is the different mode of entrance of the afferent sensory fibres. In the olfactory cortex these, represented by the olfactory tract fibres, reach the cortex from the surface; in the other areas the impulses approach the cortex from the underlying white matter, after a relay in the thalamus.

If the areas treated above are considered the primary olfactory cortex, this in man should be represented in the gyrus semilunaris which, according to Rose, corresponds to the perimygdaloid area, and in the anterior part of the gyrus ambiens, corresponding to part of the prepiriform area which is much reduced in man (cf. fig. 5). These small gyri are generally considered to be the ending place of the lateral olfactory tract fibres in man, a view in harmony with the deliberation set forth above, which also fits well with clinical observations (cf. below). When the function of any cortical area has to be inferred from structural features, there can be no doubt that the fibre connections are far more decisive than the cytoarchitecture. On this account the delimitation by von Economo of a narrow strip of koniocortex along the dorsal wall of the hippocampal fissure and in the retrosplenial region in man should not be taken as sufficient evidence for regarding these areas as primary olfactory (or even gustatory, cf. below) cortical areas, the more so since these areas belong to the allocortex and there is no decisive evidence that they receive olfactory fibres.

[1] The criticism against the distinction between homogenetic and heterogenetic cortex which has been made by certain authors, e.g. Lorente de Nó and Rose, will not be considered here.

If the peri-amygdaloid and part of the prepiriform areas are considered as the primary olfactory cortex, as is maintained by several authors, then the *entorhinal area* could with a certain right be classed with the secondary optic, acoustic and somæsthetic cortices (areas 18 and 19, 22, 5 and 7 respectively). The entorhinal area, if this view is adopted, should be considered as concerned mainly with the association and integration of olfactory impulses, reaching it from the primary olfactory cortex through association fibres, with other cortical impulses, and possibly with the finer analysis and interpretation of olfactory sensations. Unfortunately, little is known of the specific associational connections of the entorhinal area,

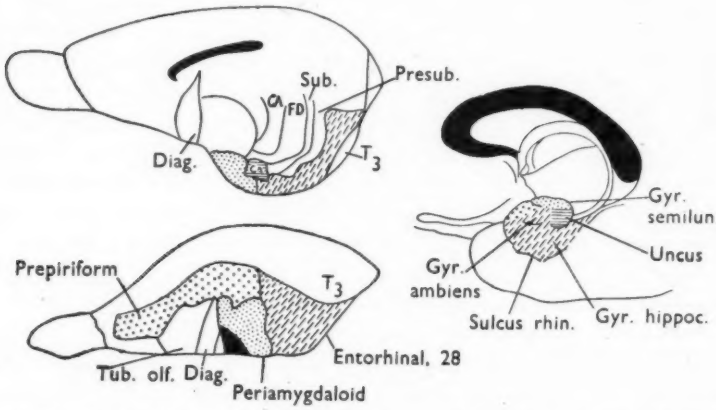

FIG. 5.—To the left two diagrams of the cortex of the rabbit as mapped out by Rose. Above medial aspect, below inferior aspect of the hemisphere. To the right an attempt is made to visualize the extent of the various areas in man, based mainly on figures and descriptions by Rose (1936). The areas are correspondingly labelled. The detailed subdivisions given by Rose are omitted.

which, difficult of access, appears not to have been studied experimentally from this point of view. Its spatial relations make it reasonable to assume that most of its associational connections are with areas of the temporal lobe. However, the functional significance of most of the areas of the temporal lobe is still obscure, and it is thus premature to venture any conjectures as to the nature of the impulses which, apart from the olfactory, may be acting on the entorhinal area and possibly influencing the hippocampus.

In man the entorhinal area occupies part of the gyrus ambiens and the entire anterior part of the gyrus hippocampi, frequently also called

gyrus entorhinalis. It has been subdivided by Rose in several sub-areas, which, however, are omitted in the diagram represented in fig. 5. The cortex of the uncus merges imperceptibly into the hippocampal formation.

From an evaluation of the anatomical features, it thus appears that the hippocampus must be considered as an effectory structure, thrown into action by impulses from the entorhinal area primarily, which again is being played upon not only by tertiary olfactory impulses reaching it from the primary olfactory cortex, but by impulses originating in other parts of the cortex as well.[1]

The conclusion that impulses other than olfactory are concerned in initiating the activity of the hippocampus receives support from some comparative anatomical data. Several comparative anatomists have drawn attention to the fact that the development of the hippocampus in mammals does not proceed parallel with the development of the sense of smell, a large hippocampus being found in several species with a very moderately developed sense of smell and a reduced olfactory apparatus. Thus man, a representative of the microsmatic mammals, possesses a very large hippocampus. Indeed, if comparisons are made between the size of the olfactory bulb and the hippocampus in various mammalian species, the extreme position is occupied by man, who has relatively (and absolutely) the largest hippocampus (Rose, 1936). In the *Macroscelididæ* the hippocampus is very large, and out of all proportion to the development of the primary and secondary olfactory areas, as pointed out by Le Gros Clark (1928). On the other hand, some observations seem to indicate that although the size of the hippocampus in mammals is partly determined by other factors than the development of the sense of olfaction, it nevertheless bears some relation to this, as might be assumed from its phylogenetic history. Thus Addison (1915) found the hippocampus reduced in the dolphin, which is said to be completely anosmatic, and in the whale (Physeter) which has no olfactory bulb and only vestigial olfactory tracts, Ries and Langworthy (1937) described the hippocampus as being diminutive. But the hippocampus as well as the fornix is still present in these anosmatic or nearly anosmatic mammals. In some human cases of arhinencephaly, the hippocampus has been found to be

[1] If it should be demonstrated by future research that the hippocampus receives direct afferent fibres from cortical areas other than the entorhinal, this would lend credence to the view adopted here. The presence of smaller contingents of afferent fibres from the cingular gyrus through the cingulum and from the induseum griseum (?) through the supracallosal striæ, to a certain extent favours the conception of the importance of non-olfactory contributions of the hippocampus.

normally developed, in spite of the complete absence of olfactory bulbs and tracts (e.g. Stewart, 1939). From a comparison with the findings in whales it appears probable, therefore, that the relation of the hippocampus to smell is still more insignificant in man than in other mammals. From a functional point of view it is worth emphasizing that the development not only of the fornix, but also of the mammillary body, the mammillothalamic tract, the anterior (more particularly the antero-ventral) nucleus of the thalamus and the cingular gyrus runs roughly parallel with the degree of development of the hippocampus. All these structures reach their peak of development in man.

Although care should be exerted in evaluating subtle differences in cytoarchitecture, it may be mentioned that according to Rose (1936 and earlier) the hippocampus as well as the entorhinal area presents an increasing differentiation in the ascending mammalian scale, the number of areal subdivisions being, for instance, larger in man than in monkeys. Rose from his study of the cytoarchitecture concludes that in man the gyrus hippocampi (including the entorhinal area) is no rudimentary structure but, so far as certain subdivisions are concerned, even a specific human organ.

Significant as are the anatomical data mentioned, they are not able to provide a definite answer to the question of the relation of the hippocampus to the sense of smell. Some physiological experiments of recent years, as well as some made by earlier authors, are, however, in agreement with the conclusions arrived at on the basis of a study of the fibre connections. The physiological experiments have partly been directed at ascertaining the presence or absence of the sense of olfaction or of olfactory reflexes when lesions have been made in different structures; they have also partly consisted of artificial stimulation of certain structures and analysis of their effects on behaviour. Experiments of the latter type are, however, equivocal, since the effects observed, such as sniffing, biting, swallowing, &c., may well be initiated by stimuli other than olfactory. In experiments where the sense of smell has to be tested some authors have employed stimuli which also act as trigeminal irritants, on which account their results are ambiguous. They will not be mentioned here.

McRioch and Brenner (1938) investigated animals deprived of all neocortex, in which only the striate body, thalamus and rhinencephalon were left. In two cats stimulation of the olfactory bulb and anterior olfactory nucleus evoked irregular chewing, swallowing and chop-licking. In other cases stimulation of basal olfactory areas elicited salivation, movement of tongue and mouth, sniffing, biting, swallowing and retching.

Although the hippocampus, and presumably the fornix, were intact in these animals, the cingular gyrus was removed, thus rendering functionless most of the efferent impulses from the hippocampus, and it appears that the hippocampal-thalamo-cingular pathway is not involved in the reactions obtained. Dusser de Barenne (1933) likewise found that highly organized smell reflexes are retained in the absence of all neocortex in cats. Bard and Marshall (1937) examined cats in which, in addition to the removal of all neocortex, a varying proportion of the hippocampus and/or the piriform lobe were damaged. Analysis of the behaviour of the cats showed that the feeding reactions appeared to be impaired in proportion to the extent of damage to the rhinencephalon. However, the sense of smell as such appeared to be preserved in all these cases. The authors state that "it is quite clear that the basal olfactory areas together with the associated ventral portions of the striatum and the lower centres with which they are connected, namely the hypothalamus, subthalamus and reticular substance of the brain-stem, are capable of elaborating feeding reactions of a highly complicated type." It appears from these experiments that the hippocampal efferents play no considerable rôle in these reflexes.

More decisive evidence has recently been brought forward by Allen, who worked on dogs, applying the method of conditioned reflexes in his study of olfaction. When a conditioned positive and negative fore-leg response to inhalation of vapours of clove oil and asafœtida, respectively, was established before the operation, the responses were not abolished after bilateral extirpation of as much as 90 per cent. of the hippocampi, or even if both hippocampi were completely destroyed (1940). The operation, furthermore, did not interfere with the transference of the fore-leg response to the other fore-leg. Transection of the fornix (1938) gave similar results. It appears from these experiments that the hippocampus and the fornix system are irrelevant for the performance of reactions which are dependent on olfactory discrimination, and that olfactory reflexes of a highly organized type (as these conditioned reflexes are) do not involve the hippocampus. The olfactory discrimination necessary for the correct response in these experiments appears to be related to the "piriform-amygdaloid areas" according to Allen's findings (1941), since extirpation of these areas bilaterally, with or without concomitant damage to the hippocampus, prevented the correct differentiation between odours of different kinds. It is remarkable, however, that the conditioned response to clove vapour was retained even in these animals, and that the

animal's capacity to select a meat packet among others not containing meat was not interfered with.

There can be little doubt from the experimental findings referred to above that even highly organized olfactory reflexes are independent of the integrity of the hippocampus. It appears, also, that reflexes not requiring discrimination are retained even in the absence of the piriform lobe. Whether the primary olfactory cortex or the entorhinal area is the part involved in olfactory discrimination can, however, not be inferred from the data available. Nor can definite conclusions be drawn concerning the pathways utilized by these reflexes. It might be assumed that they engage the amygdaloid nuclei—stria terminalis system, or, since the latter is apt to be injured when the hippocampus is extirpated, that the stria medullaris is the main efferent pathway in the reflex arc. The excitable areas of the frontal lobe are necessary for the conditioned foreleg response, as shown by Allen (1938, 1940).

It remains to be considered if findings in human beings may give any information concerning the relation of hippocampus to smell. It has already been mentioned that as far as is known no human case has been described in which olfactory disturbances have been observed following a lesion restricted to the hippocampus. Obviously such lesions will be very rare. However, it is worth recalling the common occurrence of cell loss in the hippocampus in patients suffering from epilepsy. This cell loss, due to vascular disturbances, and as a rule bilateral, is far more frequent in epileptic patients than the occurrence of uncinate fits, and it appears to bear no clear relation to impaired olfactory functions. A brief report of such patients investigated with the modern test methods for smell elaborated by Elsberg (1935) has recently been given by Elsberg and Spotnitz (1942). In 115 patients suffering from convulsive seizures, 50 per cent. showed no olfactory impairment at all. Unfortunately the authors give only a table and no details, and no definite conclusions can be drawn of the cause of impairment of the sense of smell in the other 50 per cent. Those who have had occasion to stimulate the hippocampus in conscious human beings (e.g. Penfield and Erickson, 1941) have noted no response at all from such stimulation, whereas stimulation of the olfactory bulb is followed by olfactory sensations by the patient.

No more can be learned from the post-mortem findings in patients who during life have suffered from uncinate fits. As a rule the lesion has been found, in accordance with the original report of Jackson and Beevor (1890), to involve the uncinate gyrus and more or less of the neighbouring parts

of the brain. It is extremely probable that the olfactory sensations in these cases are initiated by some sort of irritation of the primary olfactory cortex or the entorhinal area. Whether one or both of these are responsible cannot be said. It is clear that lesions in man will rarely be restricted to one of these areas alone, and as Riese (1936) states, it is not yet possible to tell which region has to be damaged in order to produce gnostic disturbances of smell. In view of the recent experimental findings the occasional occurrence of motor phenomena in the uncinate fits, such as movements of tongue and jaw, smacking of the lips, &c., cannot be taken to imply involvement of the hippocampus, and neither can similar responses reported from stimulation of the piriform lobe in animals. The inferences drawn from such experiments by Ferrier and several other earlier authors, that these reactions show the relation of the piriform lobe to olfaction, will also have to be rejected as entirely unreliable. The motor phenomena in uncinate fits can probably be explained as mediated by purely subcortical mechanisms, in analogy with the experimental findings mentioned above. Not so with the "dreamy states" usually accompanying the uncinate fits, however; these are presumably to be interpreted as mainly cortical (or cortico-hypothalamic ?) phenomena, due to a spread of irritation to other parts of the brain, and, as is well known, they may occur unaccompanied by olfactory sensations. There seems to be no reason to associate them particularly with the hippocampus.

The problem of a possible relation of the hippocampus to smell should not be left without drawing attention to some recent findings which demonstrate that the *sense of taste* is not related to the hippocampal gyrus, uncus, or hippocampus, as has been commonly assumed up to recent years. This inference appears to have been drawn mainly because the senses of smell and taste are commonly stimulated simultaneously. Following the experimental establishment of fibres from the rostral part of the nucleus of the solitary tract to the thalamus (Allen, 1923) it has been recently demonstrated by combined physiological-anatomical technique by Patton, Ruch and Walker (1944) that the gustatory fibres pass to the arcuate nucleus of the thalamus, in which also the sensory impulses from the face are relayed, and from which they are projected to the cerebral cortex. This is in accordance with the clinical studies of Börnstein (1940) who found evidence that the cortical representation of taste is in the face region of the sensory cortex in the posterior central gyrus. Possibly there may be some correlation between olfactory and gustatory impulses at levels of the brain-stem, but particulars concerning the fibre connections in question are not known.

Summing up the available data concerning the relation of the hippocampus to the sense of smell, it may be stated that the relations appear to be slight and only indirect. Being a clearly efferent structure, it may be influenced to some extent by olfactory impulses, but only indirectly after these have been transmitted to the entorhinal area and presumably integrated with important impulses from other parts of the cortex. Comparative anatomical evidence shows that the hippocampus undergoes a progressive development in mammals, irrespective of the sense of smell. Physiological experiments have clearly shown that the hippocampus is not essential for olfactory discrimination, and highly organized feeding reflexes are independent of it. Findings from human cases do not provide real evidence of any olfactory function of the hippocampus, neither has it anything to do with gustatory impulses, as recent experimental and clinical experience shows.

(7) The Functional Rôle of the Hippocampus.

From the preceding account it will be seen that it cannot be denied that the hippocampus of mammals and man may have some *indirect* relation to smell. But clearly its main function must be sought for in other spheres, and the question arises whether any information is available on this point. A knowledge of the details of the afferent connections of the hippocampus, and of the afferent connections of the entorhinal area as well, is a prerequisite if this question is to be answered satisfactorily. Other data will also be necessary. Since the afferent connections are still insufficiently known, such conclusions as may be made at present have to be drawn mainly from our knowledge of the *efferent* connections of the hippocampus, in combination with what is known of the functions of the structures to which the hippocampus sends its impulses. Some inferences of a general nature may, however, be gained from comparative anatomical data, and will be mentioned first. They have been clearly reviewed by Herrick (1933).

Herrick points out that below reptiles the entire pallial field is dominated by the olfactory system, and in reptiles where a general, yet simple, cortex appears, the latter is still to a large extent in receipt of olfactory fibres, although non-olfactory fibres also contribute. Between reptiles and mammals is a large gap, and in mammals the olfactory cortex, which according to Herrick in this connection comprises the piriform cortex and the "hippocampal cortex," is sharply separated from the non-olfactory neopallial cortex. In the ascending scale of the mammals, the olfactory

cortices remain in principle the same, whereas the non-olfactory neocortex undergoes a progressive differentiation. The development of the neocortex is attributed to its receiving afferent fibres transmitting impulses from other sense organs than the olfactory, having in common the feature of being exteroceptive and localizatory, in contrast with the olfactory impulses which possess no localizing value and may be regarded as partly exteroceptive, partly interoceptive. The interoceptive nature of olfactory impulses accounts for the widespread connections of olfactory structures with others subserving such functions as feeding, nutrition and reproduction, and the constancy of the neurological patterns of these subcortical reflex connections. The exteroceptive aspect of olfaction is concerned in such aspects of behaviour as giving warning of enemies, and guiding the animal to mates and food. In these exteroceptive functions the non-localizing sense of smell enters into correlation with the exteroceptive senses when they develop. Although the latter by and by attain a dominating influence, they are not independent of olfactory impressions, but the latter are reduced to serve mainly as unspecific activators for the former. This collaboration implies an association between the different kinds of impulses, and association is a characteristic cortical function. Thus the olfactory impulses, according to Herrick, apart from influencing the internal apparatus of the body, are also of significance for the function of exteroceptive systems whose structure is organized to permit of localized responses and which are adapted to subserve adjustment to external conditions.

It remains for future research to determine to what extent the olfactory impressions may serve as activators in particular, but the view expressed by Herrick fits well with the conclusions arrived at concerning the hippocampus in the preceding section of this paper, and also with the development of the primary and secondary olfactory cortex in mammals and man. Since the efferent connections of the hippocampus are fairly well known, it will be worth while to see if data can be obtained from a study of these, which may give information on the possible functions of the hippocampus in mammals, and to see whether an analysis fits with the general conclusions drawn by Herrick.

From a functional point of view, it seems reasonable to distinguish between two groups of hippocampal efferents, two groups which appear to correspond to a certain degree, although not completely, with the distinction made by Herrick between the interoceptive and exteroceptive aspect of olfactory functions. One group is made up of the impulses

passing via the mammillary body and anterior thalamic nucleus to the cingular gyrus. The other is represented, in higher mammals at least, by quantitatively less important fibres which take different courses. They include (1) fibres via the stria medullaris to the habenula, from which the impulses may be transmitted caudally in the brain-stem; (2) fibres to the hypothalamus and pre-optic region; and (3) fibres to the septal areas. It appears reasonable to assume that through these pathways the hippocampus will be able to influence the olfactory reflexes, inhibiting or facilitating them according to the needs of the organism at the moment. The hypothalamic connections may particularly play a rôle in the regulation of autonomic functions, well known to have an important representation in the hypothalamus. The hippocampus could, accordingly, to a certain extent be considered a cortical structure concerned in regulations of autonomic activity.

Concerning the other hippocampal efferents, forming a cortico-cortical connection, it should be realized that probably not all hippocampal impulses transmitted to the mammillary body are propagated to the cingular gyrus. Although the main mass of fornix fibres terminate in the medial mammillary nucleus, and this is the origin of the mammillothalamic tract, other fornix fibres reach the lateral mammillary nucleus. From this, as well as presumably from parts of the medial nucleus, the mammillo-tegmental tract passes caudally. This implies that these impulses are probably related to reflex mechanisms, olfactory and others, mediated through the brain-stem, although, as has been seen, the hippocampal impulses appear not to be essential for these reflexes. On the other hand, impulses other than hippocampal are probably transmitted to the anterior thalamic nucleus, since at least one additional afferent path reaches the mammillary body, and indeed the medial nucleus, namely the mammillary peduncle. Thus the ascending impulses passing through the mammillo-thalamic tract are not exclusively of hippocampal origin. It has been suggested that gustatory impulses may reach the mammillary body, but nothing definite is known of the particulars of the afferent fibres to the mammillary body apart from the fornix.

Although some authors have maintained that the *mammillary bodies* (or the immediately adjacent regions) are related to the regulation of sleep, the consensus of opinion at present seems to be that the area concerned and the lesion of which causes pathological sleep is the lateral part of the posterior hypothalamus (*see* e.g. the recent paper by Nauta, 1946). Disturbances of sleep have not been noted in the physiological experiments

involving lesions of the hippocampus referred to above. From present-day knowledge of the mammillary bodies no conclusive information appears to be forthcoming which may give hints concerning the functions of the hippocampus. However, the frequent findings of pathological changes in the mammillary bodies in cases of Wernicke's syndrome and Korsakoff's psychosis should be borne in mind (for references *see* Meyer, 1944).

Neither do we know if any particular functional rôle can be attributed to the *anterior thalamic nucleus,* although some clinical cases have been described, in which lesions of this nucleus have been assumed to be responsible for emotional changes (*see* Papez, 1937). According to the recent experiments by Lashley and Sperry (1943) in rats, bilateral degeneration of the anterior thalamic nucleus does not interfere with olfactory discrimination. There is, however, reason to believe that in addition to serving as a relay station for the impulses from the medial mammillary nucleus to the cingular gyrus, some sort of interrelation between this structure and neighbouring nuclei may exist, morphologically evidenced by mutual fibre connections or collaterals given off by passing fibres. Thus there is a possibility of alteration of the cortico-cortical impulses also at this place, and it will be wise to consider that the impulses ultimately reaching the cingular gyrus cannot be regarded as being of purely hippocampal origin.

Turning finally to the *cingular gyrus* in our search for information of the nature of the hippocampal impulses, it is of interest that this part of the brain, being for a long time poorly understood, has been investigated more thoroughly in recent years. This applies particularly to cortical areas 23 and 24. It is in agreement with the functional aspects, to be mentioned presently, that the anterior cingular area 24 is of the agranular, "motor" type, whereas the posterior cingular area 23, situated opposite the sensory cortex, is granular. Most of the area 24 has been shown by Bailey and collaborators (1944) in the macaque and chimpanzee to be one of the suppressor areas of the cortex, the stimulation of which produces, *inter alia,* relaxation of existing muscular tone. The cingular gyrus has been shown by anatomical methods to send fibres to the anterior thalamic nucleus (Le Gros Clark, 1932; Le Gros Clark and Boggon, 1933). By means of the strychnine method of Dusser de Barenne, Bailey and collaborators detected the existence of such fibres only from the area 23 in the macaque and possibly from the area 29 (retrosplenialis), whereas they did not find them from area 24. The area 23 sends association fibres *inter alia* to what appear to be areas 18 and 19. From area 24 abundant association fibres pass to areas 6 and 4s (Ward, Peden and Sugar, 1946.)

These, as well as other, findings clearly demonstrate that the cingular gyrus is no structural entity, and the morphological features are in good accord with the experimental physiological data, both tending to show that the anterior part is more concerned with effectory, or motor, functions, and the posterior parts more with receptory and associative functions. These statements, however, should be accepted only with due qualifications, since the functional terms applied are to some extent arbitrary.

The progressive development of the cingular gyrus in the mammalian scale has been mentioned above. It reaches its greatest development in man. This feature has been difficult to reconcile with the old view that the cingular gyrus forms part of the olfactory brain, the more so since this gyrus is well developed in some nearly anosmatic mammals. In view of the conclusions reached in this review, that the hippocampus in mammals and man can bear only feeble relations to the olfactory functions, it is not astonishing that recent experimental investigations in the macaque by Smith (1945) have failed to show any evidence that olfactory functions can be attributed to this part of the brain. On stimulation of the rostral part of the cingular gyrus, area 24, Smith observed a complex response, consisting of somatic as well as autonomic phenomena. Thus vocalization, movements of the lips, alteration of respiration, cardiovascular changes and pilo-erection were observed, in addition to the suppressor response revealing itself by relaxation of existing muscular tone and cessation of somatic movements. From area 23 no response was obtained.[1]

These findings do not exclude the possibility that olfactory impulses may have some importance for the function of the cingular gyrus, but it appears that at least its more important functions are to be sought in other spheres of activity. Smith is inclined to consider this part of the brain as being related to autonomic functions, more particularly to the emotional changes, since the phenomena elicited are such as generally occur in emotional processes. This assumption is in harmony with the view, expressed earlier by Papez (1937), that the hippocampus is involved in emotion as a structure transmitting cortical impulses destined to partici-

[1] The responses observed by Smith can scarcely be mediated by the pathway cingular gyrus—thalamus—mammillary body, particularly if the area 24 does not send fibres to the thalamus as maintained by Bailey and collaborators. This descending pathway, being far less massive than the ascending, is probably to be considered as mainly engaged in modifying the ascending impulses, in analogy with the current conception of the significance of the cortico-thalamic connections in general.

pate in the emotive process to the cingular gyrus. The observations by Klüver and Bucy (1939) on monkeys in which both temporal lobes had been ablated seem to support the conclusions of Papez. Changes in emotional behaviour were among the most outstanding symptoms when the hippocampi were included in the extirpation. On the whole, the assumption that the cingular gyrus, and consequently then also the hippocampus, are related to autonomic functions, probably mainly in the cortical control of these, appears at least more reasonable than to associate this system mainly with olfactory functions. That a smaller contingent of olfactory impulses partakes in hippocampal function is, however, probable, but this does not invalidate the views expressed above. To a certain extent they are in harmony with Herrick's conception.

It appears at present not possible to approach the functions of the hippocampus more closely than this. And even the deliberations mentioned above are, as yet, purely tentative. Before a closer analysis can be attempted, much work has to be done. Not least is further knowledge of the fibre connections urgently needed. It will be of primary importance to investigate experimentally whether the hippocampus receives cortical fibres from areas apart from the entorhinal area, and the association fibres reaching this from other areas have to be mapped out. In view of the differential distribution of hippocampal afferents claimed by Cajal and Lorente de Nó it would be of interest to know the exact origin of these fibres, and furthermore whether the parts of the hippocampus receiving the different groups show a corresponding segregation as concerns their efferent fibres and their termination. A more detailed knowledge of the terminal areas of the fornix fibres will be of interest, likewise a more detailed charting of the afferent and efferent connections of the mammillary body with regard to its different nuclear groups. The connections of the cingular gyrus also deserve continued study. When all these and other anatomical and in addition physiological problems have been solved, the time will perhaps have come to comprehend to a certain extent the function of the hippocampus.[1]

[1] It should perhaps be pointed out that when in this paper mention is made of the function of any particular part of the brain, such as the hippocampus, this does not, of course, mean that the structure in question is considered as a functional unit. This mode of speaking is employed only to facilitate the presentation of the material. It is indeed doubtful whether we are entitled to consider any part of the central nervous system as a functional unit.

(8) Summary and Conclusions.

On the basis of data from the literature, a review is given of the anatomical and physiological aspects of the hippocampus of mammals, particularly as regards its alleged association with the sense of smell.

The olfactory fibres from the olfactory bulb and the anterior olfactory nucleus have not been traced to the hippocampus proper. A few fibres are found to the so-called anterior continuation of the hippocampus, which is rudimentary in mammals. The olfactory fibres appear to end only in the peri-amygdaloid and prepiriform area of the so-called piriform lobe, whereas it is doubtful if any reach its posterior part, the entorhinal area (which in man occupies most of the gyrus hippocampi). The afferent fibres to the hippocampus arise mainly from the entorhinal area, small additional contributions come from the posterior part of the cingular gyrus and probably from the induseum griseum.

All efferent fibres from the hippocampus leave the latter as the fornix. Some of its fibres end in the hypothalamus, the pre-optic region and the septal areas and the habenula, but most of them go to the medial and part of the lateral mammillary nucleus. From this a massive pathway leads through the anterior thalamic nucleus to the cingular gyrus.

From a structural point of view the hippocampus must be considered a typical effector structure, transmitting but a modest proportion of impulses ultimately olfactory in origin, integrated with others the nature of which is not yet known, to the cingular gyrus and to a lesser extent to the hypothalamic, pre-optic and septal areas and the habenula. All the latter connections are probably concerned in influencing subcortical reflexes, olfactory and others, as well as hypothalamic activity. The projection to the cerebral cortex is not understood from a functional point of view. It may be concerned in cortical control of autonomic functions.

Recent physiological experiments have yielded no support for the conception that the hippocampus has important relations to the sense of smell in mammals, nor does clinical evidence seem to favour this view.

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Notices of Recent Publications.

Medical Diseases of the Locomotor System including the Rheumatic Diseases. By E. Fletcher. E. & S. Livingstone, Edinburgh. 1947. Pp. xii + 625. With 262 illustrations, some in colour. Price 45s.

One recalls the successful little monographs written by André Léri twenty years or so ago, dealing with the problems of osteoneurology. There may well be a scope for an up-to-date presentation on such questions. Diffuse aches and pains, backache, brachial and sciatic neuralgias, vertebral rheumatism, the so-called costoclavicular syndromes all belong to a condominium of the neurologist and the rheumatologist. This volume can only be discussed here in so far as it deals with neurological matters. Nothing but praise is due to the publishers and printers for the standard of their attainment, though the colour plates are less successful than one might have desired. When dealing with chapters on specialized subjects the author enlisted the help of various contributors such as Weddell on electromyography, Copeman on fibrositis, and Mitchell on the anatomy of the locomotor system. On the whole the neurological aspect of the book is disappointing. The phraseology throughout is slipshod and often obscure. Numerous errors of emphasis can be noted, such as the enumeration of amyotrophic sclerosis and combined cord degeneration as causes of brachial neuralgia. Minor inaccuracies occur, such as "Eckhom" for "Ekbom" and "myelosclerosis" for "myosclerosis." As an example of unclear writing which might well have been omitted altogether, one may quote the following sentences . . . "Post-encephalitic Parkinsonism is rarely associated with arthritis, but much more commonly with pain referred to muscles or to the spine. It is somewhat uncertain whether the connection is as intimate as might be thought. The age incidence corresponds with that of some of the common rheumatic syndromes. In one case, for instance, there was no doubt that ankylosing spondylitis has preceded the striatal syndrome."

One cannot escape the opinion that the author should have secured a neurological collaborator, before embarking upon this monograph.

Études de psychologie médicale. (1) *Perception et langage.* (*Publications savantes de l'école libre des hautes études au Brésil*). By A. Ombredane. Atlantica Editora. Rio de Janeiro. 1944. Pp. 163. Price not stated.

Within this volume are collected a series of studies upon various aspects of aphasia and agnosia, together with a close analysis of a personal case of alexia. Two chapters deal fully with visual agnosia and with acoustic agnosia respectively, and by assembling the scattered references bring these subjects into a coherent form. Congenital word blindness is treated under the title "difficulté d'apprentis-

sage persistante de la lecture." An unorthodox essay headed "les usages du langage" elaborates Jackson's original division of speech into emotional and propositional components. Ombredane recognizes five roles or levels of speech, namely, the affective, the "ludic," the practical, the representational, and the dialectic functions. These levels bear some correspondence with the steps in the development of speech in the child, and the author sees in the logorrhœa of the manic an example of the dilapidation of language towards the inferior stage of the ludic function. The initial chapter of this book gives an appraisal of Jackson's views on aphasia, from which the author passes to a recapitulation of the ideas held by Baillairger (1865). According to these, much of the phenomena of aphasia can be ascribed to the suppression of the voluntary activity of speech, with a release of the more automatic or spontaneous qualities.

Ombredane's studies are interesting, informative and well documented, but they are not easy reading.